

*****STN Columbus*****

=> file biosis,caba,caplus,embase,japio,lifesci,medline,scisearch,uspatfull

=> e prusiner stanley/au

E1 4 PRUSINER S T/AU
E2 5 PRUSINER STANELY B/AU
E3 19 --> PRUSINER STANLEY/AU
E4 760 PRUSINER STANLEY B/AU
E5 1 PRUSINGER STANLEY B/AU
E6 1 PRUSINKI A/AU
E7 1 PRUSINKIEWICA Z/AU
E8 10 PRUSINKIEWICZ C/AU
E9 2 PRUSINKIEWICZ C A/AU
E10 3 PRUSINKIEWICZ CHRISTOPHER/AU
E11 10 PRUSINKIEWICZ E/AU
E12 2 PRUSINKIEWICZ ELIZABETH/AU

=> s e2-e5 and (prion?) and monoclonal?

L1 76 ("PRUSINER STANELY B"/AU OR "PRUSINER STANLEY"/AU OR "PRUSINER STANLEY B"/AU OR "PRUSINGER STANLEY B"/AU) AND (PRION?) AND MONOCLONAL?

=> dup rem l1

PROCESSING COMPLETED FOR L1

L2 67 DUP REM L1 (9 DUPLICATES REMOVED)

=> d bib 1-

YOU HAVE REQUESTED DATA FROM 67 ANSWERS - CONTINUE? Y/(N):y

L2 ANSWER 1 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2003:262060 CAPLUS

DN 138:268056

TI Muscle sample prepared for ***prion*** assay

IN ***Prusiner, Stanley B.*** ; Bosque, Patrick

PA The Regents of the University of California, USA

SO PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 2003027631 A2 20030403 WO 2002-US24660 20020802

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003134337 A1 20030717 US 2002-211942 20020802

PRAI US 2001-323903P P 20010920

US 2002-351525P P 20020122

L2 ANSWER 2 OF 67 USPATFULL on STN

AN 2003:295034 USPATFULL
TI Method of concentrating proteins from serum
IN ***Prusiner, Stanley B.*** , San Francisco, CA, UNITED STATES
Safar, Jiri G., Concord, CA, UNITED STATES
PA The Regents of the University of California (U.S. corporation)
PI US 2003208052 A1 20031106
AI US 2003-425129 A1 20030428 (10)
RLI Continuation of Ser. No. US 2000-670506, filed on 26 Sep 2000, PENDING
Continuation of Ser. No. US 1999-264148, filed on 5 Mar 1999, GRANTED,
Pat. No. US 6166187
DT Utility
FS APPLICATION
LREP BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO
PARK, CA, 94025
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 1136

L2 ANSWER 3 OF 67 USPATFULL on STN
AN 2003:257655 USPATFULL
TI Removal of ***prions*** from blood, plasma and other liquids
IN ***Prusiner, Stanley B.*** , San Francisco, CA, UNITED STATES
Safar, Jiri G., Walnut Creek, CA, UNITED STATES
PA The Regents of the University of California (U.S. corporation)
PI US 2003180706 A1 20030925
AI US 2003-394555 A1 20030321 (10)
RLI Continuation of Ser. No. US 2001-772841, filed on 29 Jan 2001, PENDING
Continuation of Ser. No. US 1999-235372, filed on 20 Jan 1999, GRANTED,
Pat. No. US 6221614 Continuation-in-part of Ser. No. US 1998-151057,
filed on 10 Sep 1998, ABANDONED Continuation-in-part of Ser. No. US
1998-26957, filed on 20 Feb 1998, ABANDONED Continuation-in-part of Ser.
No. US 1997-804536, filed on 21 Feb 1997, GRANTED, Pat. No. US 5891641
DT Utility
FS APPLICATION
LREP BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO
PARK, CA, 94025
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1171
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 4 OF 67 USPATFULL on STN
AN 2003:206867 USPATFULL
TI Antibodies specific for ungulate PrP
IN ***Prusiner, Stanley B.*** , San Francisco, CA, UNITED STATES
Safar, Jiri G., Walnut Creek, CA, UNITED STATES
Williamson, R. Anthony, San Diego, CA, UNITED STATES
Burton, Dennis R., La Jolla, CA, UNITED STATES
PI US 2003143224 A1 20030731
AI US 2003-355780 A1 20030130 (10)
RLI Continuation of Ser. No. US 2000-627218, filed on 27 Jul 2000, GRANTED,
Pat. No. US 6537548
DT Utility

FS APPLICATION

LREP BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO
PARK, CA, 94025

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN 9 Drawing Page(s)

LN.CNT 2123

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 5 OF 67 USPATFULL on STN

AN 2003:194526 USPATFULL

TI Muscle sample prepared for ***prion*** assay

IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES

Bosque, Patrick, Denver, CO, UNITED STATES

PI US 2003134337 A1 20030717

AI US 2002-211942 A1 20020802 (10)

PRAI US 2002-351525P 20020122 (60)

US 2001-323903P 20010920 (60)

DT Utility

FS APPLICATION

LREP BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO
PARK, CA, 94025

CLMN Number of Claims: 33

ECL Exemplary Claim: 1

DRWN 9 Drawing Page(s)

LN.CNT 1977

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 6 OF 67 USPATFULL on STN

AN 2003:4268 USPATFULL

TI Sodium dodecyl sulfate compositions for inactivating ***prions***

IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES

Supattapone, Surachai, Hanover, NH, UNITED STATES

PI US 2003004312 A1 20030102

AI US 2002-56222 A1 20020122 (10)

RLI Continuation-in-part of Ser. No. US 2001-904178, filed on 11 Jul 2001,
PENDING Continuation-in-part of Ser. No. US 2000-699284, filed on 26 Oct
2000, PENDING Continuation-in-part of Ser. No. US 2000-494814, filed on
31 Jan 2000, GRANTED, Pat. No. US 6322802 Continuation-in-part of Ser.
No. US 1999-447456, filed on 22 Nov 1999, GRANTED, Pat. No. US 6331296
Continuation-in-part of Ser. No. US 1999-322903, filed on 1 Jun 1999,
GRANTED, Pat. No. US 6214366 Continuation-in-part of Ser. No. US
1999-235372, filed on 20 Jan 1999, GRANTED, Pat. No. US 6221614
Continuation-in-part of Ser. No. US 1998-151057, filed on 10 Sep 1998,
ABANDONED Continuation-in-part of Ser. No. US 1998-26957, filed on 20
Feb 1998, ABANDONED Continuation-in-part of Ser. No. US 1997-804536,
filed on 21 Feb 1997, GRANTED, Pat. No. US 5891641

DT Utility

FS APPLICATION

LREP BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO
PARK, CA, 94025

CLMN Number of Claims: 38

ECL Exemplary Claim: 1

DRWN 12 Drawing Page(s)

LN.CNT 3471

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 7 OF 67 USPATFULL on STN
AN 2003:246844 USPATFULL
TI Method for detecting ***prions***
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Safar, Jiri, Concord, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6620629 B1 20030916
AI US 2000-699033 20001027 (9)
RLI Continuation-in-part of Ser. No. US 1999-235372, filed on 20 Jan 1999,
now patented, Pat. No. US 6221614 Continuation-in-part of Ser. No. US
1998-151057, filed on 10 Sep 1998, now abandoned Continuation-in-part of
Ser. No. US 1998-26957, filed on 20 Feb 1998, now abandoned
Continuation-in-part of Ser. No. US 1997-804536, filed on 21 Feb 1997,
now patented, Pat. No. US 5891641
DT Utility
FS GRANTED
EXNAM Primary Examiner: Scheiner, Laurie; Assistant Examiner: Parkin, Jeffrey
S.
LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1459
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 8 OF 67 USPATFULL on STN
AN 2003:209940 USPATFULL
TI Recombinant construct encoding epitope tagged PrP protein
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Telling, Glenn C., San Francisco, CA, United States
Cohen, Fred E., San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6602672 B1 20030805
AI US 2000-669516 20000925 (9)
RLI Continuation of Ser. No. US 1998-31168, filed on 26 Feb 1998, now
patented, Pat. No. US 6150583 Division of Ser. No. US 1996-660626, filed
on 6 Jun 1996, now patented, Pat. No. US 5789655, issued on 4 Aug 1998
Continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995,
now patented, Pat. No. US 5908969, issued on 1 Jun 1999
Continuation-in-part of Ser. No. US 1995-509261, filed on 31 Jul 1995,
now patented, Pat. No. US 5763740, issued on 9 Jun 1998
Continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994,
now patented, Pat. No. US 5565186, issued on 15 Aug 1996
DT Utility
FS GRANTED
EXNAM Primary Examiner: Carlson, Karen Cochrane
LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 1467

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 9 OF 67 USPATFULL on STN

AN 2003:81453 USPATFULL

TI Antibodies specific for ungulate PrP

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Safar, Jiri, Concord, CA, United States

Williamson, R. Anthony, San Diego, CA, United States

Burton, Dennis R., La Jolla, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

The Scripps Research Institute, La Jolla, CA, United States (U.S.
corporation)

PI US 6537548 B1 20030325

AI US 2000-627218 20000727 (9)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Housel, James; Assistant Examiner: Winkler, Ulrike

LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP

CLMN Number of Claims: 8

ECL Exemplary Claim: 1

DRWN 13 Drawing Figure(s); 9 Drawing Page(s)

LN.CNT 2073

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 10 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1

AN 2003:160655 BIOSIS

DN PREV200300160655

TI Conformation of PrPC on the cell surface as probed by antibodies.

AU Leclerc, Estelle; Peretz, David; Ball, Haydn; Solforosi, Laura; Legname,

Giuseppe; Safar, Jiri; Serban, Ana; ***Prusiner, Stanley B.***;

Burton, Dennis R. [Reprint Author]; Williamson, R. Anthony [Reprint
Author]

CS Department of Immunology, Scripps Research Institute, La Jolla, CA, 92037,
USA

burton@scripps.edu; anthony@scripps.edu

SO Journal of Molecular Biology, (14 February, 2003) Vol. 326, No. 2, pp.
475-483. print.

ISSN: 0022-2836 (ISSN print).

DT Article

LA English

ED Entered STN: 26 Mar 2003

Last Updated on STN: 26 Mar 2003

L2 ANSWER 11 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2002:332438 CAPLUS

DN 136:337356

TI Method of determining ***prion*** strain

IN ***Prusiner, Stanley B.***; Safar, Jiri

PA The Regents of the University of California, USA

SO PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DT Patent

LA English
FAN.CNT 13

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002035238	A1	20020502	WO 2001-US29725	20010921
WO 2002035238	C1	20021212		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 6620629	B1	20030916	US 2000-699033	20001027
AU 764888	B2	20030904	AU 2001-16671	20010125
AU 2001092981	A5	20020506	AU 2001-92981	20010921
EP 1330256	A1	20030730	EP 2001-973396	20010921
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI US 2000-699033	A	20001027		
US 1997-804536	A2	19970221		
AU 1998-61688	A3	19980220		
US 1998-26957	B2	19980220		
US 1998-151057	B2	19980910		
US 1999-235372	A2	19990120		
WO 2001-US29725	W	20010921		

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:107498 CAPLUS
DN 136:149870
TI Antibodies specific for ungulate ***prion*** proteins
IN ***Prusiner, Stanley B.*** ; Safar, Jiri; Williamson, Anthony R.; Burton, Dennis R.
PA The Regents of the University of California, USA; Scripps Research Institute
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002010335	A2	20020207	WO 2001-US22648	20010717
WO 2002010335	A3	20030710		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,				

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 6537548 B1 20030325 US 2000-627218 20000727
AU 2001075977 A5 20020213 AU 2001-75977 20010717
US 2003143224 A1 20030731 US 2003-355780 20030130
PRAI US 2000-627218 A 20000727
WO 2001-US22648 W 20010717

L2 ANSWER 13 OF 67 USPATFULL on STN
AN 2002:272456 USPATFULL
TI Antibodies specific for native PrPSc
IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES
Williamson, R. Anthony, San Diego, CA, UNITED STATES
Burton, Dennis R., La Jolla, CA, UNITED STATES
PI US 2002150571 A1 20021017
US 6562341 B2 20030513
AI US 2001-943906 A1 20010830 (9)
RLI Continuation of Ser. No. US 2000-550374, filed on 13 Apr 2000, PENDING
Continuation of Ser. No. US 1998-36579, filed on 6 Mar 1998, PATENTED
Division of Ser. No. US 1996-713939, filed on 13 Sep 1996, PATENTED
Continuation-in-part of Ser. No. US 1995-528104, filed on 14 Sep 1995,
ABANDONED
DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS, LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 12 Drawing Page(s)
LN.CNT 2374
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 14 OF 67 USPATFULL on STN
AN 2002:227919 USPATFULL
TI Assay for disease related conformation of a protein and isolating same
IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES
Safar, Jiri G., Walnut Creek, CA, UNITED STATES
PI US 2002123072 A1 20020905
AI US 2002-47431 A1 20020114 (10)
RLI Continuation of Ser. No. US 2001-754443, filed on 3 Jan 2001, PENDING
Continuation of Ser. No. US 1998-169574, filed on 9 Oct 1998, GRANTED,
Pat. No. US 6214565 Continuation of Ser. No. US 1998-26967, filed on 20
Feb 1998, GRANTED, Pat. No. US 5977324
DT Utility
FS APPLICATION
LREP BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO
PARK, CA, 94025
CLMN Number of Claims: 27
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1643
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 15 OF 67 USPATFULL on STN
AN 2002:78209 USPATFULL

TI Method of sterilizing
IN ***Prusiner, Stanley B.*** , San Francisco, CA, UNITED STATES
Supattapone, Surachai, San Francisco, CA, UNITED STATES
Scott, Michael R., San Francisco, CA, UNITED STATES
PI US 2002041862 A1 20020411
US 6517855 B2 20030211
AI US 2001-956705 A1 20010919 (9)
RLI Continuation of Ser. No. US 2000-494814, filed on 31 Jan 2000, GRANTED,
Pat. No. US 6322802 Continuation-in-part of Ser. No. US 1999-447456,
filed on 22 Nov 1999, PENDING Continuation-in-part of Ser. No. US
1999-322903, filed on 1 Jun 1999, GRANTED, Pat. No. US 6214366
DT Utility
FS APPLICATION
LREP Karl Bozicevic, Bozicevic, Field and Francis LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 1727
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 16 OF 67 USPATFULL on STN
AN 2002:78206 USPATFULL
TI Antiseptic compositions for inactivating ***prions***
IN ***Prusiner, Stanley B.*** , San Francisco, CA, UNITED STATES
Supattapone, Surachai, Hanover, NH, UNITED STATES
PI US 2002041859 A1 20020411
AI US 2001-904178 A1 20010711 (9)
RLI Continuation-in-part of Ser. No. US 2000-699284, filed on 26 Oct 2000,
PENDING Continuation-in-part of Ser. No. US 2000-494814, filed on 31 Jan
2000, GRANTED, Pat. No. US 6322802 Continuation-in-part of Ser. No. US
1999-447456, filed on 22 Nov 1999, PENDING Continuation-in-part of Ser.
No. US 1999-322903, filed on 1 Jun 1999, GRANTED, Pat. No. US 6214366
Continuation-in-part of Ser. No. US 1999-235372, filed on 20 Jan 1999,
GRANTED, Pat. No. US 6221614 Continuation-in-part of Ser. No. US
1998-151057, filed on 10 Sep 1998, ABANDONED Continuation-in-part of
Ser. No. US 1998-26957, filed on 20 Feb 1998, ABANDONED
Continuation-in-part of Ser. No. US 1997-804536, filed on 21 Feb 1997,
GRANTED, Pat. No. US 5891641
DT Utility
FS APPLICATION
LREP Karl Bozicevic, Bozicevic, Field and Francis LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 12 Drawing Page(s)
LN.CNT 3354
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 17 OF 67 USPATFULL on STN
AN 2002:8938 USPATFULL
TI Models of ***prion*** disease
IN ***Prusiner, Stanley B.*** , San Francisco, CA, UNITED STATES
Korth, Carsten, San Francisco, CA, UNITED STATES
PI US 2002004938 A1 20020110

AI US 2001-895963 A1 20010628 (9)
RLI Continuation of Ser. No. US 1999-318888, filed on 26 May 1999, PENDING
DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS, LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1413
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 18 OF 67 USPATFULL on STN
AN 2002:3842 USPATFULL
TI Assay for specific strains of multiple disease related conformations of
a protein
IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES
Safar, Jiri G., Concord, CA, UNITED STATES
Cohen, Fred E., San Francisco, CA, UNITED STATES
PI US 2002001817 A1 20020103
US 6617119 B2 20030909
AI US 2001-901865 A1 20010709 (9)
RLI Continuation of Ser. No. US 1998-151057, filed on 10 Sep 1998, PENDING
Continuation-in-part of Ser. No. US 1998-26957, filed on 20 Feb 1998,
ABANDONED Continuation-in-part of Ser. No. US 1997-804536, filed on 21
Feb 1997, GRANTED, Pat. No. US 5891641
DT Utility
FS APPLICATION
LREP Karl Bozicevic, Bozicevic, Field and Francis LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 19 Drawing Page(s)
LN.CNT 2676
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 19 OF 67 USPATFULL on STN
AN 2002:174785 USPATFULL
TI Assay for compounds which affect conformationally altered proteins
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Supattapone, Surachai, San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6419916 B1 20020716
AI US 1999-406972 19990928 (9)
RLI Continuation-in-part of Ser. No. US 1999-322903, filed on 1 Jun 1999,
now patented, Pat. No. US 6214366
DT Utility
FS GRANTED
EXNAM Primary Examiner: Levy, Neil S.
LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 1807

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 20 OF 67 USPATFULL on STN

AN 2002:81024 USPATFULL

TI Antibodies specific for native PrPSc

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Williamson, R. Anthony, San Diego, CA, United States

Burton, Dennis R., La Jolla, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

The Scripps Research Institute, La Jolla, CA, United States (U.S.
corporation)

PI US 6372214 B1 20020416

AI US 2000-550374 20000413 (9)

RLI Continuation of Ser. No. US 1998-36579, filed on 6 Mar 1998 Division of
Ser. No. US 1996-713939, filed on 13 Sep 1996, now patented, Pat. No. US
5846533, issued on 8 Dec 1998 Continuation-in-part of Ser. No. US
1995-528104, filed on 14 Sep 1995, now abandoned

DT Utility

FS GRANTED

EXNAM Primary Examiner: Swartz, Rodney P

LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 21 Drawing Figure(s); 12 Drawing Page(s)

LN.CNT 2518

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 21 OF 67 USPATFULL on STN

AN 2002:69781 USPATFULL

TI Inhibitors of ***prion*** formation

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Cohen, Fred E., San Francisco, CA, United States

James, Thomas L., Nicasio, CA, United States

Kaneko, Kiyotoshi, Kodaira, JAPAN

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6365359 B1 20020402

AI US 1999-439921 19991112 (9)

RLI Continuation-in-part of Ser. No. US 1997-868162, filed on 2 Jun 1997,
now patented, Pat. No. US 5962669 Continuation-in-part of Ser. No. US
1998-76606, filed on 12 May 1998

DT Utility

FS GRANTED

EXNAM Primary Examiner: Carlson, Karen Cochrane

LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP

CLMN Number of Claims: 1

ECL Exemplary Claim: 1

DRWN 9 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 1443

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 22 OF 67 USPATFULL on STN

AN 2001:155837 USPATFULL

TI PrP-like gene
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Tremblay, Patrick, San Francisco, CA, United States
Moore, Richard, San Francisco, CA, United States
Westaway, David, Etobicoke, Canada
Hood, Leroy E., Seattle, WA, United States
Lee, Inyoul, Seattle, WA, United States
PI US 2001021771 A1 20010913
AI US 2001-799760 A1 20010305 (9)
RLI Continuation of Ser. No. US 1999-309317, filed on 11 May 1999, PENDING
DT Utility
FS APPLICATION
LREP Dianna L. DeVore, BOZICEVIC, FIELD & FRANCIS LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 26
ECL Exemplary Claim: 1
DRWN 8 Drawing Page(s)
LN.CNT 2588
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 23 OF 67 USPATFULL on STN
AN 2001:155835 USPATFULL
TI Somatic cells with ablated PrP gene and methods of use
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
PI US 2001021769 A1 20010913
AI US 2001-829507 A1 20010409 (9)
RLI Continuation of Ser. No. US 1998-220265, filed on 22 Dec 1998, ABANDONED
Continuation-in-part of Ser. No. US 1996-740947, filed on 5 Nov 1996,
GRANTED, Pat. No. US 5834593
DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1251
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 24 OF 67 USPATFULL on STN
AN 2001:134006 USPATFULL
TI Assay for disease related conformation of a protein and isolating same
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PI US 2001014455 A1 20010816
US 6406864 B2 20020618
AI US 2001-754443 A1 20010103 (9)
RLI Continuation of Ser. No. US 1998-169574, filed on 9 Oct 1998, GRANTED,
Pat. No. US 6214565
DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 27
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 1618
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 25 OF 67 USPATFULL on STN
AN 2001:100201 USPATFULL
TI Removal of ***prions*** from blood, plasma and other liquids
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PI US 2001005578 A1 20010628
AI US 2001-772841 A1 20010129 (9)
RLI Continuation of Ser. No. US 1999-235372, filed on 20 Jan 1999, GRANTED,
Pat. No. US 6221614 Continuation-in-part of Ser. No. US 1998-151057,
filed on 10 Sep 1998, PENDING Continuation-in-part of Ser. No. US
1998-26957, filed on 20 Feb 1998, ABANDONED Continuation-in-part of Ser.
No. US 1997-804536, filed on 21 Feb 1997, GRANTED, Pat. No. US 5891641
DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road,
Suite 200, Menlo Park, CA, 94025
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1170
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 26 OF 67 USPATFULL on STN
AN 2001:88925 USPATFULL
TI Assay for disease related conformation of a protein
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PI US 2001001061 A1 20010510
AI US 2000-731419 A1 20001205 (9)
RLI Continuation of Ser. No. US 1998-26957, filed on 20 Feb 1998, PENDING
Continuation-in-part of Ser. No. US 1997-804536, filed on 21 Feb 1997,
GRANTED, Pat. No. US 5891641
DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 14 Drawing Page(s)
LN.CNT 2288
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 27 OF 67 USPATFULL on STN
AN 2001:231048 USPATFULL
TI Food additives which affect conformationally altered proteins
IN ***Prusiner, Stanley B.***, 400 Pacheco St., San Francisco, CA,
United States 94116
Supattapone, Surachai, 225 Buckingham Way #702, San Francisco, CA,
United States 94132
Scott, Michael R., 1200 Clayton St., #9, San Francisco, CA, United
States 94114

PI US 6331296 B1 20011218
AI US 1999-447456 19991122 (9)
RLI Continuation-in-part of Ser. No. US 1999-322903, filed on 1 Jun 1999,
now patented, Pat. No. US 6214366
DT Utility
FS GRANTED
EXNAM Primary Examiner: Levy, Neil S.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1764
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 28 OF 67 USPATFULL on STN
AN 2001:214671 USPATFULL
TI Method of sterilizing
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Supattapone, Surachai, San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6322802 B1 20011127
AI US 2000-494814 20000131 (9)
RLI Continuation-in-part of Ser. No. US 1999-447456, filed on 22 Nov 1999
Continuation-in-part of Ser. No. US 1999-322903, filed on 1 Jun 1999,
now patented, Pat. No. US 6214366
DT Utility
FS GRANTED
EXNAM Primary Examiner: Levy, Neil S.
LREP Bozicevic, KarlBozicevic, Field & Francis LLP
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1702
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 29 OF 67 USPATFULL on STN
AN 2001:157792 USPATFULL
TI Antibodies specific for native PrPSc
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Williamson, R. Anthony, San Diego, CA, United States
Burton, Dennis R., La Jolla, CA, United States
PA The Scripps Research Institute, La Jolla, CA, United States (U.S.
corporation)
PI US 6290954 B1 20010918
AI US 1998-36579 19980306 (9)
RLI Division of Ser. No. US 1996-713939, filed on 13 Sep 1996, now patented,
Pat. No. US 5846533 Continuation-in-part of Ser. No. US 1995-528104,
filed on 14 Sep 1995, now abandoned
DT Utility
FS GRANTED
EXNAM Primary Examiner: Swartz, Rodney P.
LREP Bozicevic, Karl, DeVore, Dianna L.Bozicevic, Field & Francis LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1

DRWN 21 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 2513
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 30 OF 67 USPATFULL on STN
AN 2001:136771 USPATFULL
TI PRP-like gene
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Tremblay, Patrick, San Francisco, CA, United States
Moore, Richard, San Francisco, CA, United States
Westaway, David, Etobicoke, Canada
Hood, Leroy E., Seattle, WA, United States
Lee, Inyoul, Seattle, WA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
The University of Washington, Seattle, WA, United States (U.S.
corporation)
Governing Council of the University of Toronto, Toronto, Canada
(non-U.S. corporation)
PI US 6277970 B1 20010821
AI US 1999-309317 19990511 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Carlson, Karen Cochrane; Assistant Examiner: Tu,
Stephen
LREP DeVore, Dianna L.Bozicevic, Field & Francis LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 2588
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 31 OF 67 USPATFULL on STN
AN 2001:59636 USPATFULL
TI Removal of ***prions*** from blood, plasma and other liquids
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6221614 B1 20010424
AI US 1999-235372 19990120 (9)
RLI Continuation-in-part of Ser. No. US 1998-151057, filed on 10 Sep 1998
Continuation-in-part of Ser. No. US 1998-26957, filed on 20 Feb 1998
Continuation-in-part of Ser. No. US 1997-804536, filed on 21 Feb 1997,
now patented, Pat. No. US 5891641, issued on 6 Apr 1999
DT Utility
FS Granted
EXNAM Primary Examiner: Marschel, Ardin H.; Assistant Examiner: Ogihara, Nancy
LREP Bozicevic, KarlBozicevic, Field & Francis LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1255
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 32 OF 67 USPATFULL on STN
AN 2001:51789 USPATFULL
TI Assay for disease related conformation of a protein and isolating same
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6214565 B1 20010410
AI US 1998-169574 19981009 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Swartz, Rodney P.
LREP Bozicevic, Karl, DeVore, Dianna L.Bozicevic, Field & Francis LLP
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1675
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 33 OF 67 USPATFULL on STN
AN 2001:51590 USPATFULL
TI Clearance and inhibition of conformationally altered proteins
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Supattapone, Surachai, San Francisco, CA, United States
Scott, Michael, San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6214366 B1 20010410
AI US 1999-322903 19990601 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Levy, Neil S.
LREP DeVore, Dianna L.Bozicevic, Field and Francis LLP
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1037
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 34 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2
AN 2001:370992 BIOSIS
DN PREV200100370992
TI Cryptic epitopes in N-terminally truncated ***prion*** protein are
exposed in the full-length molecule: Dependence of conformation on pH.
AU Matsunaga, Yoichi; Peretz, David; Williamson, Anthony; Burton, Dennis;
Mehlhorn, Ingrid; Groth, Darlene; Cohen, Fred E.; ***Prusiner, Stanley***
*** B.*** ; Baldwin, Michael A. [Reprint author]
CS University of California, San Francisco, CA, 94143-0446, USA
mikeab@itsa.ucsf.edu
SO Proteins, (August 1, 2001) Vol. 44, No. 2, pp. 110-118. print.
CODEN: PSFGY. ISSN: 0887-3585.
DT Article
LA English
ED Entered STN: 8 Aug 2001

Last Updated on STN: 19 Feb 2002

L2 ANSWER 35 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2000:628298 CAPLUS

DN 133:205090

TI Blood serum sample treatment with complexing agent for isolation of
prions and PrPSc

IN ***Prusiner, Stanley B.*** ; Safar, Jiri G.

PA Regents of the University of California, USA

SO PCT Int. Appl., 38 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO	2000052197	A1	20000908	WO	2000-US5259	20000228
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W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US	6166187	A	20001226	US	1999-264148	19990305
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NZ	513670	A	20010928	NZ	2000-513670	20000228
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EP	1159446	A1	20011205	EP	2000-912087	20000228
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

BR	2000008619	A	20020716	BR	2000-8619	20000228
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JP	2002538468	T2	20021112	JP	2000-602807	20000228
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US	2003208052	A1	20031106	US	2003-425129	20030428
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PRAI US 1999-264148 A 19990305

WO 2000-US5259 W 20000228

US 2000-670506 A1 20000926

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 36 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2000:513896 CAPLUS

DN 133:109923

TI Removal of ***prions*** from blood, plasma and other liquids using
prion complexing agents

IN ***Prusiner, Stanley B.*** ; Safar, Jiri G.

PA Regents of the University of California, USA

SO PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 13

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO	2000043782	A2	20000727	WO	1999-US30167	19991217
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WO 2000043782 A3 20010118

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6221614 B1 20010424 US 1999-235372 19990120

EP 1145013 A2 20011017 EP 1999-968494 19991217

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

BR 9916932 A 20011030 BR 1999-16932 19991217

JP 2002539081 T2 20021119 JP 2000-595152 19991217

AU 764888 B2 20030904 AU 2001-16671 20010125

PRAI US 1999-235372 A 19990120

US 1997-804536 A2 19970221

AU 1998-61688 A3 19980220

US 1998-26957 A2 19980220

US 1998-151057 A2 19980910

WO 1999-US30167 W 19991217

L2 ANSWER 37 OF 67 USPATFULL on STN

AN 2000:174813 USPATFULL

TI Method of concentrating ***prion*** proteins in blood samples

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Safar, Jiri G., Concord, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6166187 20001226

AI US 1999-264148 19990305 (9)

DT Utility

FS Granted

EXNAM Primary Examiner: Le, Long V.; Assistant Examiner: Gabel, Gailene R.

LREP Bozicevic, KarlBozicevic, Field & Francis LLP

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 5 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 1102

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 38 OF 67 USPATFULL on STN

AN 2000:157631 USPATFULL

TI Transgenic animals expressing artificial epitope-tagged proteins

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Telling, Glenn C., San Francisco, CA, United States

Cohen, Fred E., San Francisco, CA, United States

Scott, Michael R., San Francisco, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6150583 20001121

AI US 1998-31168 19980226 (9)

RLI Division of Ser. No. US 1996-660626, filed on 6 Jun 1996, now patented,

Pat. No. US 5789655 which is a continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995, now patented, Pat. No. US 5908969 which is a continuation-in-part of Ser. No. US 1995-509261, filed on 31 Jul 1995, now patented, Pat. No. US 5763740 which is a continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994, now patented, Pat. No. US 5565186

DT Utility

FS Granted

EXNAM Primary Examiner: Carlson, Karen Cochrane

LREP Bozicevic, KarlBozicevic, Field & Francis LLP

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 1472

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 39 OF 67 USPATFULL on STN

AN 2000:13000 USPATFULL

TI ***Prion*** protein standard and method of making same

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6020537 20000201

AI US 1998-199523 19981125 (9)

RLI Continuation-in-part of Ser. No. US 1997-935363, filed on 22 Sep 1997 which is a continuation-in-part of Ser. No. US 1996-692892, filed on 30 Jul 1996, now patented, Pat. No. US 5792901 which is a continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995, now patented, Pat. No. US 5908969 which is a continuation-in-part of Ser. No. US 1995-509261, filed on 31 Jul 1995, now patented, Pat. No. US 5763740 which is a continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994, now patented, Pat. No. US 5565186

DT Utility

FS Granted

EXNAM Primary Examiner: Campell, Bruce R.; Assistant Examiner: Baker, Anne-Marie

LREP DeVore, Dianna L.Bozicevic, Field & Francis LLP

CLMN Number of Claims: 31

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1796

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 40 OF 67 USPATFULL on STN

AN 1999:137472 USPATFULL

TI Process for concentrating protein with disease-related conformation

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Safar, Jiri G., Concord, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 5977324 19991102

AI US 1998-26967 19980220 (9)

DT Utility

FS Granted

EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Delacroix-M,

Cybill

LREP Bozicevic, KarlBozicevic, Field & Francis LLP
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1370
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 41 OF 67 USPATFULL on STN
AN 1999:121570 USPATFULL
TI Nucleic acid encoding ***prion*** protein variant
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Cohen, Fred E., San Francisco, CA, United States
James, Thomas L., Nicasio, CA, United States
Kaneko, Kiyotoshi, San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5962669 19991005
AI US 1997-868162 19970602 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Longton, Enrique
D.

LREP Bozicevic, KarlBozicevic, Field & Francis LLP
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 17 Drawing Figure(s); 15 Drawing Page(s)
LN.CNT 2993
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 42 OF 67 USPATFULL on STN
AN 1999:63442 USPATFULL
TI Method of detecting ***prions*** in a sample and transgenic animal
used for same
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
Telling, Glenn, San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5908969 19990601
AI US 1995-521992 19950831 (8)
RLI Continuation-in-part of Ser. No. US 1995-509261, filed on 31 Jul 1995,
now patented, Pat. No. US 5763740 which is a continuation-in-part of
Ser. No. US 1994-242188, filed on 13 May 1994, now patented, Pat. No. US
5565186

DT Utility
FS Granted
EXNAM Primary Examiner: Stanton, Brian R.; Assistant Examiner: Beckerleg, Anne
Marie S.

LREP Bozicevic, KarlBozicevic & Reed LLP
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 2687
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 43 OF 67 USPATFULL on STN
AN 1999:43389 USPATFULL
TI Assay for disease related conformation of a protein
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5891641 19990406
AI US 1997-804536 19970221 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Woodward, Michael P.; Assistant Examiner: Zeman, Mary
K.
LREP Bozicevic, KarlBozicevic & Reed LLP
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 11 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1990
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 44 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3
AN 2000:55212 BIOSIS
DN PREV200000055212
TI Antibody binding defines a structure for an epitope that participates in
the PrPC fwdarw PrPSc conformational change.
AU Kanyo, Zoltan F.; Pan, Keh-Ming; Williamson, R. Anthony; Burton, Dennis
R.; ***Prusiner, Stanley B.*** ; Fletterick, Robert J.; Cohen, Fred E.
[Reprint author]
CS Departments of Cellular and Molecular Pharmacology Biochemistry and
Biophysics and Medicine, University of California, San Francisco, CA, USA
SO Journal of Molecular Biology, (Nov. 5, 1999) Vol. 293, No. 4, pp. 855-863.
print.
CODEN: JMOBAK. ISSN: 0022-2836.
DT Article
LA English
ED Entered STN: 3 Feb 2000
Last Updated on STN: 3 Jan 2002

L2 ANSWER 45 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:605069 CAPLUS
DN 129:200174
TI Assay for disease-related conformation of a protein
IN ***Prusiner, Stanley B.*** ; Safar, Jiri G.
PA The Regents of the University of California, USA
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9837411	A1	19980827	WO 1998-US2992	19980220
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,				

DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG,
 KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
 NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
 UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
 FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
 GA, GN, ML, MR, NE, SN, TD, TG
 US 5891641 A 19990406 US 1997-804536 19970221
 AU 9861688 A1 19980909 AU 1998-61688 19980220
 AU 725844 B2 20001019
 EP 970372 A1 20000112 EP 1998-906471 19980220
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, FI
 BR 9807600 A 20000222 BR 1998-7600 19980220
 JP 2001516448 T2 20010925 JP 1998-536064 19980220
 MX 9907739 A 20000430 MX 1999-7739 19990820
 AU 764888 B2 20030904 AU 2001-16671 20010125
 PRAI US 1997-804536 A 19970221
 AU 1998-61688 A3 19980220
 WO 1998-US2992 W 19980220
 RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 46 OF 67 USPATFULL on STN
 AN 1998:153857 USPATFULL
 TI Antibodies specific for native PrP.sup.Sc
 IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
 Williamson, R. Anthony, San Diego, CA, United States
 Burton, Dennis R., La Jolla, CA, United States
 PA The Regents of the University of California, Oakland, CA, United States
 (U.S. corporation)
 The Scripps Research Institute, La Jolla, CA, United States (U.S.
 corporation)
 PI US 5846533 19981208
 AI US 1996-713939 19960913 (8)
 RLI Continuation-in-part of Ser. No. US 1995-528104, filed on 14 Sep 1995,
 now abandoned
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Swartz, Rodney
 P.
 LREP Bozicevic & Reed LLP, Bozicevic, Karl
 CLMN Number of Claims: 11
 ECL Exemplary Claim: 1
 DRWN 21 Drawing Figure(s); 12 Drawing Page(s)
 LN.CNT 3059
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 47 OF 67 USPATFULL on STN
 AN 1998:139024 USPATFULL
 TI Soluble form of PrP.sup.SC which is insoluble in native form
 IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
 Cohen, Fred E., San Francisco, CA, United States
 Muramoto, Tamaki, San Francisco, CA, United States
 PA The Regents of the University of California, Oakland, CA, United States

(U.S. corporation)
PI US 5834593 19981110
AI US 1996-740947 19961105 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Sun-Hoffman, Lin
LREP Bozicevic & Reed LLP, Bozicevic, Karl
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1331
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 48 OF 67 USPATFULL on STN
AN 1998:95670 USPATFULL
TI Detecting ***prions*** in a sample and ***prion*** preparation
and transgenic animal used for same
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
Telling, Glenn C., San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5792901 19980811
AI US 1996-692892 19960730 (8)
RLI Continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995
which is a continuation-in-part of Ser. No. US 1995-509261, filed on 31
Jul 1995 which is a continuation-in-part of Ser. No. US 1994-242188,
filed on 13 May 1994, now patented, Pat. No. US 5565186
DT Utility
FS Granted
EXNAM Primary Examiner: Stanton, Brian R.
LREP Bozicevic & Reed LLP, Bozicevic, Karl
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 3351
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 49 OF 67 USPATFULL on STN
AN 1998:92267 USPATFULL
TI Transgenic animals expressing artificial epitope-tagged proteins
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Telling, Glenn C., San Francisco, CA, United States
Cohen, Fred E., San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
PA The Regents of the University of California, Alameda, CA, United States
(U.S. corporation)
PI US 5789655 19980804
AI US 1996-660626 19960606 (8)
RLI Continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995
which is a continuation-in-part of Ser. No. US 1995-509261, filed on 31
Jul 1995 which is a continuation-in-part of Ser. No. US 1994-242188,
filed on 13 May 1994, now patented, Pat. No. US 5565186, issued on 15
Aug 1996
DT Utility

FS Granted
EXNAM Primary Examiner: Chambers, Jasmine C.; Assistant Examiner: Clark,
Deborah J. R.
LREP Bozicevic & Reed LLP, Bozicevic, Esq., Karl
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1409
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 50 OF 67 USPATFULL on STN
AN 1998:65517 USPATFULL
TI Method of detecting ***prions*** in a sample and transgenic animal
used for same
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
Telling, Glenn, San Francisco, CA, United States
PA The Regents of the University of California, Alameda, CA, United States
(U.S. corporation)
PI US 5763740 19980609
AI US 1995-509261 19950731 (8)
RLI Continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994,
now patented, Pat. No. US 5565186

DT Utility
FS Granted
EXNAM Primary Examiner: Stanton, Brian R.
LREP Bozicevic & Reed LLP, Bozicevic, Karl
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 2464
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 51 OF 67 USPATFULL on STN
AN 1998:51444 USPATFULL
TI Formation and use of ***prion*** protein (PRP) complexes
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Kaneko, Kivotoshi, San Francisco, CA, United States
Cohen, Fred E., San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5750361 19980512
AI US 1995-556823 19951102 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Hutzell, Paula K.; Assistant Examiner: Navarro, Mark
LREP Bozicevic, KarlBozicevic & Reed LLP
CLMN Number of Claims: 27
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1295
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 52 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 4

AN 1998:491190 BIOSIS
DN PREV199800491190
TI Mapping the ***prion*** protein using recombinant antibodies.
AU Williamson, R. Anthony; Peretz, David; Pinilla, Clemencia; Ball, Hadyn;
Bastidas, Raiza R.; Rozenshteyn, Roman; Houghten, Richard A.;
Prusiner, Stanley B. ; Burton, Dennis R. [Reprint author]
CS Dep. Immunol., Scripps Res. Inst., 10550 N. Torrey Pines Rd., La Jolla, CA
92037, USA
SO Journal of Virology, (Nov., 1998) Vol. 72, No. 11, pp. 9413-9418. print.
CODEN: JOVIAM. ISSN: 0022-538X.
DT Article
LA English
ED Entered STN: 18 Nov 1998
Last Updated on STN: 18 Nov 1998

L2 ANSWER 53 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:429542 CAPLUS
DN 127:47438
TI ***Prion*** protein peptides PrP and assays for PrPSc and inhibitors
of PrPSc formation
IN ***Prusiner, Stanley B.*** ; Kaneko, Kiyotoshi; Cohen, Fred E.
PA Regents of the University of California, USA
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9716728	A1	19970509	WO 1996-US17462	19961028
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI US 5750361 A 19980512 US 1995-556823 19951102 AU 9676012 A1 19970522 AU 1996-76012 19961028 AU 715659 B2 20000210 JP 2000500439 T2 20000118 JP 1997-517540 19961028 EP 1007964 A1 20000614 EP 1996-938699 19961028 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI BR 9611428 A 20001024 BR 1996-11428 19961028 PRAI US 1995-556823 A 19951102 WO 1996-US17462 W 19961028				

L2 ANSWER 54 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:317787 CAPLUS
DN 126:290385
TI Antibodies specific for native PrPSc for therapy and analysis
IN ***Prusiner, Stanley B.*** ; Williamson, R. Anthony; Burton, Dennis R.
PA Regents of the University of California, USA
SO PCT Int. Appl., 100 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9710505	A1	19970320	WO 1996-US14840	19960913
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
CA 2231409	AA	19970320	CA 1996-2231409	19960913
CA 2231409	C	20030211		
AU 9670735	A1	19970401	AU 1996-70735	19960913
AU 707484	B2	19990708		
EP 852011	A1	19980708	EP 1996-931599	19960913
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000500005	T2	20000111	JP 1997-512175	19960913
BR 9610580	A	20001024	BR 1996-10580	19960913
PRAI US 1995-528104	A	19950914		
WO 1996-US14840	W	19960913		

L2 ANSWER 55 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 5

AN 1998:205874 BIOSIS

DN PREV199800205874

TI ***Prion*** protein expression in Chinese hamster ovary cells using a glutamine synthetase selection and amplification system.

AU Blochberger, Thomas C.; Cooper, Carol; Peretz, David; Tatzelt, Jorg; Griffith, O. Hayes; Baldwin, Michael A.; ***Prusiner, Stanley B.***
[Reprint author]

CS Dep. Neurol., Univ. Calif. San Francisco, San Francisco, CA 94143, USA

SO Protein Engineering, (Dec., 1997) Vol. 10, No. 12, pp. 1465-1473. print.

CODEN: PRENE9. ISSN: 0269-2139.

DT Article

LA English

ED Entered STN: 11 May 1998

Last Updated on STN: 11 May 1998

L2 ANSWER 56 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 6

AN 1997:221417 BIOSIS

DN PREV199799513133

TI N-terminally tagged ***prion*** protein supports ***prion*** propagation in transgenic mice.

AU Telling, Glenn C.; Tremblay, Patrick; Torchia, Marilyn; Dearmond, Stephen J.; Cohen, Fred E.; ***Prusiner, Stanley B.*** [Reprint author]

CS Dep. Neurol., Univ. Calif., San Francisco, CA 94143-0518, USA

SO Protein Science, (1997) Vol. 6, No. 4, pp. 825-833.

ISSN: 0961-8368.

DT Article

LA English
ED Entered STN: 22 May 1997
Last Updated on STN: 22 May 1997

L2 ANSWER 57 OF 67 USPATFULL on STN
AN 96:94320 USPATFULL
TI Method of detecting ***prions*** in a sample and transgenic animal
used for same
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
Telling, Glenn, San Francisco, CA, United States
PA The Regents of the University of California, Alameda, CA, United States
(U.S. corporation)
PI US 5565186 19961015
AI US 1994-242188 19940513 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Stanton, Brian R.
LREP Bozicevic, KarlFish & Richardson P.C.
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1774
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 58 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 7
AN 1996:485155 BIOSIS
DN PREV199699200411
TI Circumventing tolerance to generate autologous ***monoclonal***
antibodies to the ***prion*** protein.
AU Williamson, R. Anthony; Peretz, David; Smorodinsky, Nechama; Bastidas,
Raiza; Serban, Hana; Mehlhorn, Ingrid; Dearmond, Stephen J.;
Prusiner, Stanley B.; Burton, Dennis R. [Reprint author]
CS Dep. Immunology Molecular Biol., Scripps Res. Inst., 10550 North Torrey
Pines Road, La Jolla, CA 92037, USA
SO Proceedings of the National Academy of Sciences of the United States of
America, (1996) Vol. 93, No. 14, pp. 7279-7282.
CODEN: PNASA6. ISSN: 0027-8424.
DT Article
LA English
ED Entered STN: 24 Oct 1996
Last Updated on STN: 24 Oct 1996

L2 ANSWER 59 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 8
AN 1996:31257 BIOSIS
DN PREV199698603392
TI ***Prion*** protein (Prp) synthetic peptides induce cellular Prp to
acquire properties of the scrapie isoform.
AU Kaneko, Kiyotoshi [Reprint author]; Peretz, David [Reprint author]; Pan,
Keh-Ming; Blochberger, Thomas C. [Reprint author]; Wille, Holger [Reprint
author]; Gabizon, Ruth; Griffith, O. Hayes; Cohen, Fred E.; Baldwin,
Michael A.; ***Prusiner, Stanley B.***
CS Dep. Neurol., Univ. California, San Francisco, CA 94143, USA

SO Proceedings of the National Academy of Sciences of the United States of
America, (1995) Vol. 92, No. 24, pp. 11160-11164.
CODEN: PNASA6. ISSN: 0027-8424.

DT Article

LA English

ED Entered STN: 26 Jan 1996

Last Updated on STN: 26 Jan 1996

L2 ANSWER 60 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1992:607463 CAPLUS

DN 117:207463

TI Attempts to convert the cellular ***prion*** protein into the scrapie
isoform in cell-free systems

AU Raeber, Alex J.; Borchelt, David R.; Scott, Michael; ***Prusiner,***
*** Stanley B.***

CS Dep. Neurol., Univ. California, San Francisco, CA, 94143-0518, USA

SO Journal of Virology (1992), 66(10), 6155-63

CODEN: JOVIAM; ISSN: 0022-538X

DT Journal

LA English

L2 ANSWER 61 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 9

AN 1994:273187 BIOSIS

DN PREV199497286187

TI Chimeric ***prion*** protein expression in cultured cells and
transgenic mice.

AU Scott, Michael R.; Koehler, Ruth; Foster, Dallas; ***Prusiner, Stanley***
*** B.*** [Reprint author]

CS Dep. Neurol., HSE-781, Univ. Calif., San Francisco, CA 94143-0518, USA

SO Protein Science, (1992) Vol. 1, No. 8, pp. 986-997.

ISSN: 0961-8368.

DT Article

LA English

ED Entered STN: 24 Jun 1994

Last Updated on STN: 24 Jun 1994

L2 ANSWER 62 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1995:22148 CAPLUS

DN 122:52760

TI ***Prion*** biology

AU ***Prusiner, Stanley B.***

CS Dep. Neurol. Biochem. Biophys., Univ. California, San Francisco, CA,
94143-0518, USA

SO Prion Dis. Hum. Anim. (1992), 533-67. Editor(s): ***Prusiner, Stanley***
*** B***. Publisher: Horwood, London, UK.

CODEN: 60BWAD

DT Conference; General Review

LA English

L2 ANSWER 63 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1994:673074 CAPLUS

DN 121:273074

TI Modification and expression of ***prion*** proteins in cultured cells

AU Rogers, Mark; Taraboulos, Albert; Scott, Michael; Borchelt, David; Serban,

Dan; Gyuris, Tibor; ***Prusiner, Stanley B.***
CS Dep. Neurol., Univ. California, San Francisco, CA, 94143, USA
SO Prion Dis. Hum. Anim. (1992), 457-69. Editor(s): ***Prusiner, Stanley***
*** B*** . Publisher: Horwood, London, UK.
CODEN: 60BWAD
DT Conference; General Review
LA English

L2 ANSWER 64 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1990:176299 CAPLUS
DN 112:176299
TI Three hamster species with different scrapie incubation times and
neuropathological features encode distinct ***prion*** proteins
AU Lowenstein, Daniel H.; Butler, Darel A.; Westaway, David; McKinley,
Michael P.; DeArmond, Stephen J.; ***Prusiner, Stanley B.***
CS Dep. Neurol., Univ. California, San Francisco, CA, 94143-0518, USA
SO Molecular and Cellular Biology (1990), 10(3), 1153-63
CODEN: MCEBD4; ISSN: 0270-7306
DT Journal
LA English

L2 ANSWER 65 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1988:588177 CAPLUS
DN 109:188177
TI Immunoaffinity purification and neutralization of scrapie ***prion***
infectivity
AU Gabizon, Ruth; McKinley, Michael P.; Groth, Darlene; ***Prusiner,***
*** Stanley B.***
CS Dep. Neurol., Univ. California, San Francisco, CA, 94143, USA
SO Proceedings of the National Academy of Sciences of the United States of
America (1988), 85(18), 6617-21
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English

L2 ANSWER 66 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1988:565993 CAPLUS
DN 109:165993
TI Purification and properties of the cellular and scrapie hamster
prion proteins
AU Turk, Eric; Teplow, David B.; Hood, Leroy E.; ***Prusiner, Stanley B.***
CS Dep. Neurol., Univ. California, San Francisco, CA, 94143-0518, USA
SO European Journal of Biochemistry (1988), 176(1), 21-30
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English

L2 ANSWER 67 OF 67 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1986:551182 CAPLUS
DN 105:151182
TI ***Monoclonal*** antibodies to the cellular and scrapie ***prion***
proteins
AU Barry, Ronald A.; ***Prusiner, Stanley B.***
CS Dep. Neurol., Univ. California, San Francisco, CA, USA
SO Journal of Infectious Diseases (1986), 154(3), 518-21

CODEN: JIDIAQ; ISSN: 0022-1899
DT Journal
LA English

=> file uspatfull

=> e prusiner stanley/in

E1 1 PRUSIK RENEE S/IN
E2 10 PRUSIK THADDEUS/IN
E3 0 --> PRUSINER STANLEY/IN
E4 34 PRUSINER STANLEY B/IN
E5 1 PRUSINOWSKI JOHN C/IN
E6 1 PRUSINSKI JAN R/IN
E7 3 PRUSINSKI RICHARD C/IN
E8 3 PRUSINSKI RONALD G/IN
E9 2 PRUSINSKI THOMAS/IN
E10 1 PRUSIS ALLEN W/IN
E11 2 PRUSKI EDWARD M/IN
E12 2 PRUSKI JOHN A/IN

=> s e4

L1 34 "PRUSINER STANLEY B"/IN

=> d bib 1-

YOU HAVE REQUESTED DATA FROM 34 ANSWERS - CONTINUE? Y/(N):y

L1 ANSWER 1 OF 34 USPATFULL

AN 2002:174785 USPATFULL

TI Assay for compounds which affect conformationally altered proteins

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Supattapone, Surachai, San Francisco, CA, United States

Scott, Michael R., San Francisco, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6419916 B1 20020716

AI US 1999-406972 19990928 (9)

RLI Continuation-in-part of Ser. No. US 1999-322903, filed on 1 Jun 1999,
now patented, Pat. No. US 6214366

DT Utility

FS GRANTED

EXNAM Primary Examiner: Levy, Neil S.

LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP

CLMN Number of Claims: 8

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 1807

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 2 OF 34 USPATFULL

AN 2002:81024 USPATFULL

TI Antibodies specific for native PrPSc

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Williamson, R. Anthony, San Diego, CA, United States

Burton, Dennis R., La Jolla, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

The Scripps Research Institute, La Jolla, CA, United States (U.S.
corporation)

PI US 6372214 B1 20020416

AI US 2000-550374 20000413 (9)

RLI Continuation of Ser. No. US 1998-36579, filed on 6 Mar 1998 Division of

Ser. No. US 1996-713939, filed on 13 Sep 1996, now patented, Pat. No. US 5846533, issued on 8 Dec 1998 Continuation-in-part of Ser. No. US 1995-528104, filed on 14 Sep 1995, now abandoned

DT Utility

FS GRANTED

EXNAM Primary Examiner: Swartz, Rodney P

LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 21 Drawing Figure(s); 12 Drawing Page(s)

LN.CNT 2518

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 3 OF 34 USPATFULL

AN 2002:78209 USPATFULL

TI Method of sterilizing

IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES

Supattapone, Surachai, San Francisco, CA, UNITED STATES

Scott, Michael R., San Francisco, CA, UNITED STATES

PI US 2002041862 A1 20020411

AI US 2001-956705 A1 20010919 (9)

RLI Continuation of Ser. No. US 2000-494814, filed on 31 Jan 2000, GRANTED,

Pat. No. US 6322802 Continuation-in-part of Ser. No. US 1999-447456,

filed on 22 Nov 1999, PENDING Continuation-in-part of Ser. No. US

1999-322903, filed on 1 Jun 1999, GRANTED, Pat. No. US 6214366

DT Utility

FS APPLICATION

LREP Karl Bozicevic, Bozicevic, Field and Francis LLP, Suite 200, 200

Middlefield Road, Menlo Park, CA, 94025

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 1727

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 4 OF 34 USPATFULL

AN 2002:78206 USPATFULL

TI Antiseptic compositions for inactivating prions

IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES

Supattapone, Surachai, Hanover, NH, UNITED STATES

PI US 2002041859 A1 20020411

AI US 2001-904178 A1 20010711 (9)

RLI Continuation-in-part of Ser. No. US 2000-699284, filed on 26 Oct 2000,

PENDING Continuation-in-part of Ser. No. US 2000-494814, filed on 31 Jan

2000, GRANTED, Pat. No. US 6322802 Continuation-in-part of Ser. No. US

1999-447456, filed on 22 Nov 1999, PENDING Continuation-in-part of Ser.

No. US 1999-322903, filed on 1 Jun 1999, GRANTED, Pat. No. US 6214366

Continuation-in-part of Ser. No. US 1999-235372, filed on 20 Jan 1999,

GRANTED, Pat. No. US 6221614 Continuation-in-part of Ser. No. US

1998-151057, filed on 10 Sep 1998, ABANDONED Continuation-in-part of

Ser. No. US 1998-26957, filed on 20 Feb 1998, ABANDONED

Continuation-in-part of Ser. No. US 1997-804536, filed on 21 Feb 1997,

GRANTED, Pat. No. US 5891641

DT Utility

FS APPLICATION

LREP Karl Bozicevic, Bozicevic, Field and Francis LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN 12 Drawing Page(s)

LN.CNT 3354

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 5 OF 34 USPATFULL

AN 2002:69781 USPATFULL

TI Inhibitors of prion formation

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Cohen, Fred E., San Francisco, CA, United States

James, Thomas L., Nicasio, CA, United States

Kaneko, Kiyotoshi, Kodaira, JAPAN

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6365359 B1 20020402

AI US 1999-439921 19991112 (9)

RLI Continuation-in-part of Ser. No. US 1997-868162, filed on 2 Jun 1997,
now patented, Pat. No. US 5962669 Continuation-in-part of Ser. No. US
1998-76606, filed on 12 May 1998

DT Utility

FS GRANTED

EXNAM Primary Examiner: Carlson, Karen Cochrane

LREP Bozicevic, Karl, Bozicevic, Field & Francis LLP

CLMN Number of Claims: 1

ECL Exemplary Claim: 1

DRWN 9 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 1443

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 6 OF 34 USPATFULL

AN 2002:8938 USPATFULL

TI Models of prion disease

IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES

Korth, Carsten, San Francisco, CA, UNITED STATES

PI US 2002004938 A1 20020110

AI US 2001-895963 A1 20010628 (9)

RLI Continuation of Ser. No. US 1999-318888, filed on 26 May 1999, PENDING

DT Utility

FS APPLICATION

LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS, LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1413

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 7 OF 34 USPATFULL

AN 2002:3842 USPATFULL

TI Assay for specific strains of multiple disease related conformations of
a protein

IN ***Prusiner, Stanley B.***, San Francisco, CA, UNITED STATES

Safar, Jiri G., Concord, CA, UNITED STATES
Cohen, Fred E., San Francisco, CA, UNITED STATES

PI US 2002001817 A1 20020103

AI US 2001-901865 A1 20010709 (9)

RLI Continuation of Ser. No. US 1998-151057, filed on 10 Sep 1998, PENDING
Continuation-in-part of Ser. No. US 1998-26957, filed on 20 Feb 1998,
ABANDONED Continuation-in-part of Ser. No. US 1997-804536, filed on 21
Feb 1997, GRANTED, Pat. No. US 5891641

DT Utility

FS APPLICATION

LREP Karl Bozicevic, Bozicevic, Field and Francis LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN 19 Drawing Page(s)

LN.CNT 2676

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 8 OF 34 USPATFULL

AN 2001:231048 USPATFULL

TI Food additives which affect conformationally altered proteins

IN ***Prusiner, Stanley B.***, 400 Pacheco St., San Francisco, CA,
United States 94116
Supattapone, Surachai, 225 Buckingham Way #702, San Francisco, CA,
United States 94132
Scott, Michael R., 1200 Clayton St., #9, San Francisco, CA, United
States 94114

PI US 6331296 B1 20011218

AI US 1999-447456 19991122 (9)

RLI Continuation-in-part of Ser. No. US 1999-322903, filed on 1 Jun 1999,
now patented, Pat. No. US 6214366

DT Utility

FS GRANTED

EXNAM Primary Examiner: Levy, Neil S.

CLMN Number of Claims: 11

ECL Exemplary Claim: 1

DRWN 1 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 1764

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 9 OF 34 USPATFULL

AN 2001:214671 USPATFULL

TI Method of sterilizing

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Supattapone, Surachai, San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6322802 B1 20011127

AI US 2000-494814 20000131 (9)

RLI Continuation-in-part of Ser. No. US 1999-447456, filed on 22 Nov 1999
Continuation-in-part of Ser. No. US 1999-322903, filed on 1 Jun 1999,
now patented, Pat. No. US 6214366

DT Utility

FS GRANTED

EXNAM Primary Examiner: Levy, Neil S.
LREP Bozicevic, KarlBozicevic, Field & Francis LLP
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1702
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 10 OF 34 USPATFULL
AN 2001:157792 USPATFULL
TI Antibodies specific for native PrPSc
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Williamson, R. Anthony, San Diego, CA, United States
Burton, Dennis R., La Jolla, CA, United States
PA The Scripps Research Institute, La Jolla, CA, United States (U.S.
corporation)
PI US 6290954 B1 20010918
AI US 1998-36579 19980306 (9)
RLI Division of Ser. No. US 1996-713939, filed on 13 Sep 1996, now patented,
Pat. No. US 5846533 Continuation-in-part of Ser. No. US 1995-528104,
filed on 14 Sep 1995, now abandoned
DT Utility
FS GRANTED

EXNAM Primary Examiner: Swartz, Rodney P.
LREP Bozicevic, Karl, DeVore, Dianna L.Bozicevic, Field & Francis LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 2513
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 11 OF 34 USPATFULL
AN 2001:155837 USPATFULL
TI PrP-like gene
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Tremblay, Patrick, San Francisco, CA, United States
Moore, Richard, San Francisco, CA, United States
Westaway, David, Etobicoke, Canada
Hood, Leroy E., Seattle, WA, United States
Lee, Inyoul, Seattle, WA, United States
PI US 2001021771 A1 20010913
AI US 2001-799760 A1 20010305 (9)
RLI Continuation of Ser. No. US 1999-309317, filed on 11 May 1999, PENDING
DT Utility
FS APPLICATION

LREP Dianna L. DeVore, BOZICEVIC, FIELD & FRANCIS LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 26
ECL Exemplary Claim: 1
DRWN 8 Drawing Page(s)
LN.CNT 2588
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 12 OF 34 USPATFULL
AN 2001:155835 USPATFULL

TI Somatic cells with ablated PrP gene and methods of use
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
PI US 2001021769 A1 20010913
AI US 2001-829507 A1 20010409 (9)
RLI Continuation of Ser. No. US 1998-220265, filed on 22 Dec 1998, ABANDONED
Continuation-in-part of Ser. No. US 1996-740947, filed on 5 Nov 1996,
GRANTED, Pat. No. US 5834593
DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1251
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 13 OF 34 USPATFULL
AN 2001:136771 USPATFULL
TI PRP-like gene
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Tremblay, Patrick, San Francisco, CA, United States
Moore, Richard, San Francisco, CA, United States
Westaway, David, Etobicoke, Canada
Hood, Leroy E., Seattle, WA, United States
Lee, Inyoul, Seattle, WA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
The University of Washington, Seattle, WA, United States (U.S.
corporation)
Governing Council of the University of Toronto, Toronto, Canada
(non-U.S. corporation)
PI US 6277970 B1 20010821
AI US 1999-309317 19990511 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Carlson, Karen Cochrane; Assistant Examiner: Tu,
Stephen
LREP DeVore, Dianna L.Bozicevic, Field & Francis LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 2588
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 14 OF 34 USPATFULL
AN 2001:134006 USPATFULL
TI Assay for disease related conformation of a protein and isolating same
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PI US 2001014455 A1 20010816
US 6406864 B2 20020618
AI US 2001-754443 A1 20010103 (9)
RLI Continuation of Ser. No. US 1998-169574, filed on 9 Oct 1998, GRANTED,
Pat. No. US 6214565

DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 27
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1618
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 15 OF 34 USPATFULL
AN 2001:100201 USPATFULL
TI Removal of prions from blood, plasma and other liquids
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PI US 2001005578 A1 20010628
AI US 2001-772841 A1 20010129 (9)
RLI Continuation of Ser. No. US 1999-235372, filed on 20 Jan 1999, GRANTED,
Pat. No. US 6221614 Continuation-in-part of Ser. No. US 1998-151057,
filed on 10 Sep 1998, PENDING Continuation-in-part of Ser. No. US
1998-26957, filed on 20 Feb 1998, ABANDONED Continuation-in-part of Ser.
No. US 1997-804536, filed on 21 Feb 1997, GRANTED, Pat. No. US 5891641

DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road,
Suite 200, Menlo Park, CA, 94025
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1170
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 16 OF 34 USPATFULL
AN 2001:88925 USPATFULL
TI Assay for disease related conformation of a protein
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PI US 2001001061 A1 20010510
AI US 2000-731419 A1 20001205 (9)
RLI Continuation of Ser. No. US 1998-26957, filed on 20 Feb 1998, PENDING
Continuation-in-part of Ser. No. US 1997-804536, filed on 21 Feb 1997,
GRANTED, Pat. No. US 5891641

DT Utility
FS APPLICATION
LREP Karl Bozicevic, BOZICEVIC, FIELD & FRANCIS LLP, Suite 200, 200
Middlefield Road, Menlo Park, CA, 94025
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 14 Drawing Page(s)
LN.CNT 2288
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 17 OF 34 USPATFULL
AN 2001:59636 USPATFULL
TI Removal of prions from blood, plasma and other liquids

IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6221614 B1 20010424
AI US 1999-235372 19990120 (9)
RLI Continuation-in-part of Ser. No. US 1998-151057, filed on 10 Sep 1998
Continuation-in-part of Ser. No. US 1998-26957, filed on 20 Feb 1998
Continuation-in-part of Ser. No. US 1997-804536, filed on 21 Feb 1997,
now patented, Pat. No. US 5891641, issued on 6 Apr 1999
DT Utility
FS Granted
EXNAM Primary Examiner: Marschel, Ardin H.; Assistant Examiner: Ogihara, Nancy
LREP Bozicevic, KarlBozicevic, Field & Francis LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1255
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 18 OF 34 USPATFULL
AN 2001:51789 USPATFULL
TI Assay for disease related conformation of a protein and isolating same
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6214565 B1 20010410
AI US 1998-169574 19981009 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Swartz, Rodney P.
LREP Bozicevic, Karl, DeVore, Dianna L.Bozicevic, Field & Francis LLP
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1675
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 19 OF 34 USPATFULL
AN 2001:51590 USPATFULL
TI Clearance and inhibition of conformationally altered proteins
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Supattapone, Surachai, San Francisco, CA, United States
Scott, Michael, San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 6214366 B1 20010410
AI US 1999-322903 19990601 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Levy, Neil S.
LREP DeVore, Dianna L.Bozicevic, Field and Francis LLP
CLMN Number of Claims: 14
ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1037

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 20 OF 34 USPATFULL

AN 2000:174813 USPATFULL

TI Method of concentrating prion proteins in blood samples

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Safar, Jiri G., Concord, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6166187 20001226

AI US 1999-264148 19990305 (9)

DT Utility

FS Granted

EXNAM Primary Examiner: Le, Long V.; Assistant Examiner: Gabel, Gailene R.

LREP Bozicevic, KarlBozicevic, Field & Francis LLP

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 5 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 1102

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 21 OF 34 USPATFULL

AN 2000:157631 USPATFULL

TI Transgenic animals expressing artificial epitope-tagged proteins

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Telling, Glenn C., San Francisco, CA, United States

Cohen, Fred E., San Francisco, CA, United States

Scott, Michael R., San Francisco, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6150583 20001121

AI US 1998-31168 19980226 (9)

RLI Division of Ser. No. US 1996-660626, filed on 6 Jun 1996, now patented,
Pat. No. US 5789655 which is a continuation-in-part of Ser. No. US
1995-521992, filed on 31 Aug 1995, now patented, Pat. No. US 5908969
which is a continuation-in-part of Ser. No. US 1995-509261, filed on 31
Jul 1995, now patented, Pat. No. US 5763740 which is a
continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994,
now patented, Pat. No. US 5565186

DT Utility

FS Granted

EXNAM Primary Examiner: Carlson, Karen Cochrane

LREP Bozicevic, KarlBozicevic, Field & Francis LLP

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 1472

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 22 OF 34 USPATFULL

AN 2000:13000 USPATFULL

TI Prion protein standard and method of making same

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6020537 20000201

AI US 1998-199523 19981125 (9)

RLI Continuation-in-part of Ser. No. US 1997-935363, filed on 22 Sep 1997
which is a continuation-in-part of Ser. No. US 1996-692892, filed on 30
Jul 1996, now patented, Pat. No. US 5792901 which is a
continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995,
now patented, Pat. No. US 5908969 which is a continuation-in-part of
Ser. No. US 1995-509261, filed on 31 Jul 1995, now patented, Pat. No. US
5763740 which is a continuation-in-part of Ser. No. US 1994-242188,
filed on 13 May 1994, now patented, Pat. No. US 5565186

DT Utility

FS Granted

EXNAM Primary Examiner: Campell, Bruce R.; Assistant Examiner: Baker,
Anne-Marie

LREP DeVore, Dianna L.Bozicevic, Field & Francis LLP

CLMN Number of Claims: 31

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1796

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 23 OF 34 USPATFULL

AN 1999:170827 USPATFULL

TI Detecting cow, sheep and human prions in a sample and transgenic mice
used for same

IN ***Prusiner, Stanley B.***, San Francisco, CA, United States

Scott, Michael R., San Francisco, CA, United States

Telling, Glenn C., San Francisco, CA, United States

PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)

PI US 6008435 19991228

AI US 1997-935363 19970922 (8)

RLI Continuation-in-part of Ser. No. US 1996-692892, filed on 30 Jul 1996,
now patented, Pat. No. US 5792901 which is a continuation-in-part of
Ser. No. US 1995-521992, filed on 31 Aug 1995, now patented, Pat. No. US
5908969 which is a continuation-in-part of Ser. No. US 1995-509261,
filed on 31 Jul 1995, now patented, Pat. No. US 5763740 which is a
continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994,
now patented, Pat. No. US 5565186, issued on 15 Oct 1996

DT Utility

FS Granted

EXNAM Primary Examiner: Campell, Bruce R.; Assistant Examiner: Baker,
Anne-Marie

LREP Bozicevic, Field & Francis LLP

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1676

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 24 OF 34 USPATFULL

AN 1999:137472 USPATFULL

TI Process for concentrating protein with disease-related conformation

IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5977324 19991102
AI US 1998-26967 19980220 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Delacroix-M,
Cybille
LREP Bozicevic, KarlBozicevic, Field & Francis LLP
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1370
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 25 OF 34 USPATFULL
AN 1999:121570 USPATFULL
TI Nucleic acid encoding prion protein variant
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Cohen, Fred E., San Francisco, CA, United States
James, Thomas L., Nicasio, CA, United States
Kaneko, Kiyotoshi, San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5962669 19991005
AI US 1997-868162 19970602 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Longton, Enrique
D.
LREP Bozicevic, KarlBozicevic, Field & Francis LLP
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 17 Drawing Figure(s); 15 Drawing Page(s)
LN.CNT 2993
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 26 OF 34 USPATFULL
AN 1999:63442 USPATFULL
TI Method of detecting prions in a sample and transgenic animal used for
same
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
Telling, Glenn, San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5908969 19990601
AI US 1995-521992 19950831 (8)
RLI Continuation-in-part of Ser. No. US 1995-509261, filed on 31 Jul 1995,
now patented, Pat. No. US 5763740 which is a continuation-in-part of
Ser. No. US 1994-242188, filed on 13 May 1994, now patented, Pat. No. US
5565186
DT Utility

FS Granted
EXNAM Primary Examiner: Stanton, Brian R.; Assistant Examiner: Beckerleg, Anne Marie S.
LREP Bozicevic, KarlBozicevic & Reed LLP
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 2687
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 27 OF 34 USPATFULL
AN 1999:43389 USPATFULL
TI Assay for disease related conformation of a protein
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Safar, Jiri G., Concord, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5891641 19990406
AI US 1997-804536 19970221 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Woodward, Michael P.; Assistant Examiner: Zeman, Mary K.
LREP Bozicevic, KarlBozicevic & Reed LLP
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 11 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1990
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 28 OF 34 USPATFULL
AN 1998:153857 USPATFULL
TI Antibodies specific for native PrP.sup.Sc
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Williamson, R. Anthony, San Diego, CA, United States
Burton, Dennis R., La Jolla, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
The Scripps Research Institute, La Jolla, CA, United States (U.S. corporation)
PI US 5846533 19981208
AI US 1996-713939 19960913 (8)
RLI Continuation-in-part of Ser. No. US 1995-528104, filed on 14 Sep 1995, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Housel, James C.; Assistant Examiner: Swartz, Rodney P.
LREP Bozicevic & Reed LLP, Bozicevic, Karl
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 3059
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 29 OF 34 USPATFULL
AN 1998:139024 USPATFULL
TI Soluble form of PrP.sup.SC which is insoluble in native form
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Cohen, Fred E., San Francisco, CA, United States
Muramoto, Tamaki, San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5834593 19981110
AI US 1996-740947 19961105 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Sun-Hoffman, Lin
LREP Bozicevic & Reed LLP, Bozicevic, Karl
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1331
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 30 OF 34 USPATFULL
AN 1998:95670 USPATFULL
TI Detecting prions in a sample and prion preparation and transgenic animal
used for same
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
Telling, Glenn C., San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5792901 19980811
AI US 1996-692892 19960730 (8)
RLI Continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995
which is a continuation-in-part of Ser. No. US 1995-509261, filed on 31
Jul 1995 which is a continuation-in-part of Ser. No. US 1994-242188,
filed on 13 May 1994, now patented, Pat. No. US 5565186
DT Utility
FS Granted
EXNAM Primary Examiner: Stanton, Brian R.
LREP Bozicevic & Reed LLP, Bozicevic, Karl
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 3351
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 31 OF 34 USPATFULL
AN 1998:92267 USPATFULL
TI Transgenic animals expressing artificial epitope-tagged proteins
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Telling, Glenn C., San Francisco, CA, United States
Cohen, Fred E., San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
PA The Regents of the University of California, Alameda, CA, United States
(U.S. corporation)
PI US 5789655 19980804

AI US 1996-660626 19960606 (8)
RLI Continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995
which is a continuation-in-part of Ser. No. US 1995-509261, filed on 31
Jul 1995 which is a continuation-in-part of Ser. No. US 1994-242188,
filed on 13 May 1994, now patented, Pat. No. US 5565186, issued on 15
Aug 1996
DT Utility
FS Granted
EXNAM Primary Examiner: Chambers, Jasmine C.; Assistant Examiner: Clark,
Deborah J. R.
LREP Bozicevic & Reed LLP, Bozicevic, Esq., Karl
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1409
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 32 OF 34 USPATFULL
AN 1998:65517 USPATFULL
TI Method of detecting prions in a sample and transgenic animal used for
same
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
Telling, Glenn, San Francisco, CA, United States
PA The Regents of the University of California, Alameda, CA, United States
(U.S. corporation)
PI US 5763740 19980609
AI US 1995-509261 19950731 (8)
RLI Continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994,
now patented, Pat. No. US 5565186
DT Utility
FS Granted
EXNAM Primary Examiner: Stanton, Brian R.
LREP Bozicevic & Reed LLP, Bozicevic, Karl
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 2464
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 33 OF 34 USPATFULL
AN 1998:51444 USPATFULL
TI Formation and use of prion protein (PRP) complexes
IN ***Prusiner, Stanley B.***, San Francisco, CA, United States
Kaneko, Kivotoshi, San Francisco, CA, United States
Cohen, Fred E., San Francisco, CA, United States
PA The Regents of the University of California, Oakland, CA, United States
(U.S. corporation)
PI US 5750361 19980512
AI US 1995-556823 19951102 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Hutzell, Paula K.; Assistant Examiner: Navarro, Mark
LREP Bozicevic, KarlBozicevic & Reed LLP
CLMN Number of Claims: 27

ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1295
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 34 OF 34 USPATFULL
AN 96:94320 USPATFULL
TI Method of detecting prions in a sample and transgenic animal used for
same
IN ***Prusiner, Stanley B.*** , San Francisco, CA, United States
Scott, Michael R., San Francisco, CA, United States
Telling, Glenn, San Francisco, CA, United States
PA The Regents of the University of California, Alameda, CA, United States
(U.S. corporation)
PI US 5565186 19961015
AI US 1994-242188 19940513 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Stanton, Brian R.
LREP Bozicevic, KarlFish & Richardson P.C.
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1774
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> logoff y
STN INTERNATIONAL LOGOFF AT 16:47:42 ON 13 AUG 2002

*****STN Columbus*****

FILE 'HOME' ENTERED AT 19:05:45 ON 19 NOV 2003

=> file biosis,caba,caplus,embase,japio,lifesci,medline,scisearch,uspatfull

=> e kurano yoshihiro/au

E1 69 KURANO YOSHIKI/AU
E2 1 KURANO YOSHIDO/AU
E3 78 --> KURANO YOSHIHIRO/AU
E4 89 KURANO YOSHITO/AU
E5 2 KURANO YUKI/AU
E6 37 KURANO YUKIO/AU
E7 8 KURANO YUTAKA/AU
E8 6 KURANOBU/AU
E9 23 KURANOBU K/AU
E10 1 KURANOBU KAZUHIKO/AU
E11 2 KURANOBU KAZUO/AU
E12 1 KURANOBU KOJI/AU

=> s e3 and prion?

L1 2 "KURANO YOSHIHIRO"/AU AND PRION?

=> dup rem l1

PROCESSING COMPLETED FOR L1

L2 2 DUP REM L1 (0 DUPLICATES REMOVED)

=> d bib ab 1-

YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L2 ANSWER 1 OF 2 USPATFULL on STN

AN 2003:213736 USPATFULL

TI Anti-abnormal type ***prion*** monoclonal antibody, process for
producing the same, and immunoassay using the same

IN ***Kurano, Yoshihiro***, Chuo-ku, JAPAN

Umetani, Atsushi, Chuo-ku, JAPAN

Miyakoshi, Hideo, Chuo-ku, JAPAN

Yanagiya, Takayuki, Chuo-ku, JAPAN

PI US 2003148374 A1 20030807

AI US 2001-5120 A1 20011207 (10)

DT Utility

FS APPLICATION

LREP BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 567

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A monoclonal antibody which enables to distinguish the abnormal type
prion from the normal type ***prion***, as well as
production process thereof, is disclosed. The anti-abnormal type
prion monoclonal antibody of the invention reacts with abnormal
type ***prion*** by antigen-antibody reaction but does not
substantially react with normal type ***prion*** by antigen-antibody
reaction. The anti-abnormal type ***prion*** monoclonal antibody of
the invention may be obtained by immunizing an animal with an immunogen
including a peptide containing a plurality of regions in the abnormal
type ***prion***, which regions are discontinuous each other in
primary amino acid sequence of the abnormal type ***prion***.

L2 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2002:446128 CAPLUS

DN 137:19391

TI Monoclonal antibody for distinguishing abnormal type ***prion*** from
normal type ***prion*** and immunoassay kit
IN ***Kurano, Yoshihiro*** ; Umetani, Atsushi; Miyakoshi, Hideo; Yanagiya,
Takayuki

PA Fujirebio Inc., Japan

SO Eur. Pat. Appl., 12 pp.

CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI EP 1213301	A2	20020612	EP 2001-310310	20011210
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EP 1213301	A3	20020619		
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

WO 2002046236	A1	20020613	WO 2001-JP10721	20011207
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W: AE, AG, AL, AM, AT, AZ, BA, BB, BG, BR, BY, BZ, CH, CN, CO, CR,
CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, PH, PL, PT, RO, RU, SD,
SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001097138	A5	20020711	AU 2001-97138	20011207
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US 2003148374	A1	20030807	US 2001-5120	20011207
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NZ 515982	A	20030926	NZ 2001-515982	20011207
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PRAI JP 2000-374145 A 20001208

AB A monoclonal antibody which enables to distinguish the abnormal type
prion from the normal type ***prion*** , as well as prodn.
process thereof, is disclosed. The anti-abnormal type ***prion***
monoclonal antibody of the invention reacts with abnormal type
prion by antigen-antibody reaction but does not substantially
react with normal type ***prion*** by antigen-antibody reaction. The
anti-abnormal type ***prion*** monoclonal antibody of the invention
may be obtained by immunizing an animal with an immunogen including a
peptide contg. a plurality of regions in the abnormal type ***prion***
, which regions are discontinuous each other in primary amino acid
sequence of the abnormal type ***prion*** .

=> e umetani atsushi/au

E1	1	UMETANI AKIJI/AU
E2	3	UMETANI AKIRA/AU
E3	17	--> UMETANI ATSUSHI/AU
E4	1	UMETANI ATUSHI/AU
E5	2	UMETANI CHIEKO/AU
E6	5	UMETANI EIJI/AU
E7	17	UMETANI H/AU
E8	1	UMETANI HAKUBUMI/AU
E9	1	UMETANI HARUFUMI/AU
E10	9	UMETANI HARUKI/AU
E11	1	UMETANI HARUSHIGE/AU
E12	2	UMETANI HIDEHIRO/AU

=> s e3-e4

L3 18 ("UMETANI ATSUSHI"/AU OR "UMETANI ATUSHI"/AU)

=> dup rem l3

PROCESSING COMPLETED FOR L3

L4 14 DUP REM L3 (4 DUPLICATES REMOVED)

=> d bib ab 1-

YOU HAVE REQUESTED DATA FROM 14 ANSWERS - CONTINUE? Y/(N):y

L4 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2003:884553 CAPLUS

TI The anti- abnormal type prion monoclonal antibody and its production method and immunity measuring method of the abnormal type prion protein which uses that [Machine Translation].

IN Shinagawa, Shinichi; Horiuchi, Motohiro; ***Umetani, Atsushi***

PA Obihiro University of Agriculture and Veterinary Medicine, Japan; Fujirebio, Inc.

SO Jpn. Kokai Tokkyo Koho, 8 pp.

CODEN: JKXXAF

DT Patent

LA Japanese

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI JP 2003321498	A2	20031111	JP 2002-129003	20020430
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PRAI JP 2002-129003		20020430		
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AB [Machine Translation of Descriptors]. Offer the monoclonal antibody which recognizes only the abnormal type prion protein. The abnormal type prion protein was designated as the corresponding antigen, the normal type prion protein the anti- abnormal type prion monoclonal antibody or the antigen connection characteristic fragment which does not react substantially was offered. The abnormal type prion protein was designated as the corresponding antigen, the normal type prion protein the anti- abnormal type prion monoclonal antibody which does not react substantially was for the first time offered. Because the monoclonal antibody of this invention has designated the natural abnormal type prion protein as the corresponding antigen, it is possible to measure the abnormal type prion protein in high sensitivity.

L4 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2003:349832 CAPLUS

DN 138:365135

TI Immunoassay reagent and kit for measuring abnormal-type prion, and immunoassay method for measuring abnormal-type prion using reagent or kit

IN Shinagawa, Shinichi; Horiuchi, Motohiro; Yanagitani, Takayuki; Matsui, Toshio; ***Umetani, Atsushi***

PA Fujirebio, Inc., Japan

SO Jpn. Kokai Tokkyo Koho, 9 pp.

CODEN: JKXXAF

DT Patent

LA Japanese

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI JP 2003130880	A2	20030508	JP 2001-330696	20011029
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PRAI JP 2001-330696		20011029		
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AB An immunoassay method is provided for detecting the abnormal-type prion with high sensitivity without performing a time-consuming electrophoresis operation or centrifugation operation. Also provided is an immunoassay reagent for this method, which is prepd. by immobilizing a first antibody immunol. reactive with the abnormal-type prion treated with a denaturing agent (e.g., guanidine, guanidine thiocyanate) on magnetic particles. The method comprises a process for treating a sample potentially contg. the abnormal-type prion with a surfactant, collagenase and a proteinase (e.g.,

proteinase K), a process for treating the product obtained with a denaturing agent without having a centrifuge operation, and a process for immunol. assaying the product with the immunoassay reagent.

L4 ANSWER 3 OF 14 USPATFULL on STN

AN 2003:213736 USPATFULL

TI Anti-abnormal type prion monoclonal antibody, process for producing the same, and immunoassay using the same

IN Kurano, Yoshihiro, Chuo-ku, JAPAN

Umetani, Atsushi, Chuo-ku, JAPAN

Miyakoshi, Hideo, Chuo-ku, JAPAN

Yanagiya, Takayuki, Chuo-ku, JAPAN

PI US 2003148374 A1 20030807

AI US 2001-5120 A1 20011207 (10)

DT Utility

FS APPLICATION

LREP BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 567

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A monoclonal antibody which enables to distinguish the abnormal type prion from the normal type prion, as well as production process thereof, is disclosed. The anti-abnormal type prion monoclonal antibody of the invention reacts with abnormal type prion by antigen-antibody reaction but does not substantially react with normal type prion by antigen-antibody reaction. The anti-abnormal type prion monoclonal antibody of the invention may be obtained by immunizing an animal with an immunogen including a peptide containing a plurality of regions in the abnormal type prion, which regions are discontinuous each other in primary amino acid sequence of the abnormal type prion.

L4 ANSWER 4 OF 14 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1

AN 2002:501866 BIOSIS

DN PREV200200501866

TI Immunoassay method of HIV-1p24 antigen and reagent therefor.

AU Yamamoto, Katsuhiko [Inventor, Reprint author]; Yoshiki, Akemi [Inventor];
Matsui, Toshio [Inventor]; ***Umetani, Atsushi*** [Inventor]

CS Tokyo, Japan

ASSIGNEE: Fujirebio Kabushiki Kaisha, Tokyo, Japan

PI US 6432633 August 13, 2002

SO Official Gazette of the United States Patent and Trademark Office Patents,
(Aug. 13, 2002) Vol. 1261, No. 2. [http://www.uspto.gov/web/menu/patdata.ht](http://www.uspto.gov/web/menu/patdata.html)
ml. e-file.

CODEN: OGUPE7. ISSN: 0098-1133.

DT Patent

LA English

ED Entered STN: 25 Sep 2002

Last Updated on STN: 25 Sep 2002

AB An immunoassay method of the HIV-1p24 antigen by sandwich method, using at least one polyclonal antibody recognizing the HIV-1p24 antigen and at least two monoclonal antibodies recognizing the HIV-1p24 antigen, is provided together with a reagent therefor, to establish more highly sensitive assay of the HIV-1p24 antigen than conventionally.

L4 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2002:446128 CAPLUS

DN 137:19391

TI Monoclonal antibody for distinguishing abnormal type prion from normal

type prion and immunoassay kit

IN Kurano, Yoshihiro; ***Umetani, Atsushi*** ; Miyakoshi, Hideo; Yanagiya, Takayuki

PA Fujirebio Inc., Japan

SO Eur. Pat. Appl., 12 pp.

CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI EP 1213301	A2	20020612	EP 2001-310310	20011210
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EP 1213301	A3	20020619		
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

WO 2002046236 A1 20020613 WO 2001-JP10721 20011207

W: AE, AG, AL, AM, AT, AZ, BA, BB, BG, BR, BY, BZ, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001097138 A5 20020711 AU 2001-97138 20011207

US 2003148374 A1 20030807 US 2001-5120 20011207

NZ 515982 A 20030926 NZ 2001-515982 20011207

PRAI JP 2000-374145 A 20001208

AB A monoclonal antibody which enables to distinguish the abnormal type prion from the normal type prion, as well as prodn. process thereof, is disclosed. The anti-abnormal type prion monoclonal antibody of the invention reacts with abnormal type prion by antigen-antibody reaction but does not substantially react with normal type prion by antigen-antibody reaction. The anti-abnormal type prion monoclonal antibody of the invention may be obtained by immunizing an animal with an immunogen including a peptide contg. a plurality of regions in the abnormal type prion, which regions are discontinuous each other in primary amino acid sequence of the abnormal type prion.

L4 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2001:78091 CAPLUS

DN 134:144217

TI Improved immunoassay method and reagent for identifying HIV-1p24 antigen

IN Yamamoto, Katsuhiko; Yoshiki, Akemi; Matsui, Toshio; ***Umetani, ***

*** Atsushi***

PA Fujirebio K. K., Japan

SO Eur. Pat. Appl., 53 pp.

CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI EP 1072888	A2	20010131	EP 2000-114953	20000719
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EP 1072888	A3	20030618		
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2001041961 A2 20010216 JP 1999-213224 19990728

US 6432633 B1 20020813 US 2000-621625 20000721

PRAI JP 1999-213224 A 19990728

AB This invention provides an improved immunoassay method (sandwich method)

for the p24 antigen of HIV-1. At least two monoclonal antibodies and a polyclonal antibodies were prepd. which recognize different region of HIV-1p24 polypeptide. The monoclonal antibodies were used to immobilize HIV-1p24 on solid phase and the Alk. phosphate (ALP) labeled polyclonal antibody is used to chemiluminescent immunoassay. This method manipulate the combination of antibodies which provides more highly sensitive assay of the HIV-1p24 antigen than conventionally.

L4 ANSWER 7 OF 14 JAPIO (C) 2003 JPO on STN
 AN 1999-333073 JAPIO
 TI PRIZE DEVICE FOR PACHINKO GAME MACHINE
 IN YAMADA TADAKATSU; MIZUNO MASANOBU; ***UMETANI ATSUSHI***
 PA HEIWA CORP
 PI JP 11333073 A 19991207 Heisei
 AI JP 1998-166332 (JP10166332 Heisei) 19980528
 PRAI JP 1998-166332 19980528
 SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1999
 AB PROBLEM TO BE SOLVED: To provide a prize device for resetting a selector plate to a posture for facilitating the flow of pachinko balls to a regular ball passage by the pachinko ball passing through a round continuation ball passage.
 SOLUTION: A linkage piece 34 rotates to allow an opening/closing plate 26 to open a large prize hole 2a when an opening/closing hole 2a. Through the rotation of the piece 34, a hook 42 rotates via a plate 40 connected to the hook 42. A selector plate 31 engaged with the hook 42 via a selector plate operating lever 44 tilts to the posture so that pachinko balls are made to easily flow to a round continuation ball passage (c). When the pachinko ball passing through the passage (c) pushes a tilting releasing lever 45, the hook 42 is rotated to release the engagement with the lever 44. Accordingly, the plate 31 is returned to the posture for making pachinko balls easily flow to a regular ball passage (b).
 COPYRIGHT: (C)1999,JPO

L4 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 2
 AN 1997:731404 CAPLUS
 DN 128:21868
 TI Antibodies for detecting emerlin
 IN Arahata, Kiichi; Kurano, Yoshihiro; ***Umetani, Atsushi***
 PA Fujirebio, Inc., Japan
 SO Jpn. Kokai Tokkyo Koho, 9 pp.
 CODEN: JKXXAF
 DT Patent
 LA Japanese
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 09278799	A2	19971028	JP 1997-36904	19970206
PRAI JP 1996-42209		19960206		

AB Monoclonal antibodies are disclosed for detecting emerlin and for diagnosing Emery-Dreifuss muscular dystrophy. These monoclonal antibodies are specific for emerlin polypeptide encoded by STA gene. Cys-Emerlin 173-188 and Cys-Emerlin 245-254 were synthesized and conjugated with keyhole limpet hemocyanin for raising monoclonal antibodies.

L4 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 3
 AN 1997:340594 CAPLUS
 DN 126:303449
 TI Stabilization of human hemoglobin in aqueous solution or during freeze-drying
 IN Nakamura, Satoru; ***Umetani, Atsushi*** ; Yanagya, Takayuki
 PA Fujirebio Kk, Japan

SO Jpn. Kokai Tokkyo Koho, 4 pp.

CODEN: JKXXAF

DT Patent

LA Japanese

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI JP 09061431	A2	19970307	JP 1995-242339	19950829
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JP 3348573	B2	20021120		
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PRAI JP 1995-242339 19950829

AB An additive selected from albumin of domestic rabbits, glycine, aspartate, and glutamate is used to stabilize human Hb during the prepn. of aq. soln. or freeze-drying. The stabilized human Hb can be used as a control for during the detection of occult blood by using immunoassay of Hb.

L4 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 4

AN 1995:958445 CAPLUS

DN 124:4477

TI Hemoglobin sampler

IN Hori, Hironobu; Kurihara, Norigi; Gotanda, Mitsushi; Yanagiya, Takayuki; ***Umetani, Atsushi***

PA Fujirebio Kabushiki Kaisha, Japan; Aubex Corp.

SO U.S., 6 pp. Cont.-in-part of U.S. Ser. No. 427,543, abandoned.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI US 5460781	A	19951024	US 1991-669079	19910312
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PRAI US 1989-427543		19891027		
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AB A Hb sampler for use with stool samples for clin. tests and diagnoses of the digestive tract diseases in mass screening, etc. by securely sampling and collecting occult Hb with water content from the stool samples without being hindered by the undigested solid content of stools. The sampler has a core member consisting of a porous fiber bundle made up of a plural no. of synthetic fibers bundled in the longitudinal direction thereof, a rod of a suitable length provided with a thermosetting synthetic resin sheath at the outer periphery of the core, one end of the rod forming a sample absorbing member with a suitable surface area and small diam. made up of the above mentioned porous fiber bundle. The sampler can quant. sample occult Hb with water from stool samples of various properties, thereby offering an easy sample method for the subject and stable specimen for tests. Thus, the utility of the test method can be fully exerted and the sampler is quite useful for clin. tests and mass health screening.

L4 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1994:206284 CAPLUS

DN 120:206284

TI Studies of thick film capacitor. The trimming methods of thick film capacitor and its electric characteristics

AU Yamamoto, Tateo; ***Umetani, Atushi*** ; Kato, Susumu; Hosoya, Tatuo

CS Shizuokaken Hamamatsu Kogyogijutsu Cent., Hamamatsu, Japan

SO Shizuoka-ken Hamamatsu Kogyo Gijutsu Senta Kenkyu Hokoku (1992), 2, 84-8

CODEN: SHKGEF; ISSN: 0916-8389

DT Journal

LA Japanese

AB The fabrication of thick film capacitors by using laser trimming is described. Two different trimming methods, the U-cut and the scan-cut, using laser radiation from a YAG laser with power of 15W, were used in trimming material for capacitors. The relation between depth of the cut

and the dielec. properties and the capacitance of the product was discussed.

L4 ANSWER 12 OF 14 JAPIO (C) 2003 JPO on STN
AN 2003-130880 JAPIO
TI REAGENT AND KIT FOR MEASURING IMMUNITY OF ABNORMAL PRION, AND METHOD OF
MEASURING IMMUNITY OF ABNORMAL PRION BY USING THE SAME
IN SHINAGAWA SHINICHI; HORIUCHI MOTOHIRO; YANAGIYA TAKAYUKI; MATSUI TOSHIO;
UMETANI ATSUSHI
PA FUJIREBIO INC
PI JP 2003130880 A 20030508 Heisei
AI JP 2001-330696 (JP2001330696 Heisei) 20011029
PRAI JP 2001-330696 20011029
SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2003
AB PROBLEM TO BE SOLVED: To provide an immunity measuring method capable of
detecting the abnormal prion with high sensitivity without performing the
electrophoretic operation and the centrifugal operation, which take much
time.
SOLUTION: This reagent for measuring the immunity of abnormal prion is
prepared by making the abnormal prion treated by a denaturing agent and a
first antibody performing antigen-antibody reaction immobilized to
magnetic particles. This method of measuring the abnormal prion includes a
process for treating a sample which may include the abnormal prion, with a
surface active agent, collagenase and protease, a process for treating the
obtained product by the denaturing agent without performing the
centrifugal operation, and a process for measuring the immunity of the
obtained product by using the reagent.
COPYRIGHT: (C)2003,JPO

L4 ANSWER 13 OF 14 JAPIO (C) 2003 JPO on STN
AN 2001-041961 JAPIO
TI IMMUNOASSAY AND REAGENT FOR HIV-1p24 ANTIGEN
IN YAMAMOTO KATSUHIKO; YOSHIKI AKEMI; MATSUI TOSHIO; ***UMETANI ATSUSHI***
PA FUJIREBIO INC
PI JP 2001041961 A 20010216 Heisei
AI JP 1999-213224 (JP11213224 Heisei) 19990728
PRAI JP 1999-213224 19990728
SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2001
AB PROBLEM TO BE SOLVED: To assay an HIV-1p24 antigen with high sensitivity
using one kind of polyclonal antibody for recognizing an HIV-1p24 antigen
and two kinds of monoclonal antibody.
SOLUTION: A polyclonal antibody having a main recognition part of HIV-1p24
antigen is employed and an HIV-1p24 antigen is purified as an immunogen.
The polyclonal antibody preferably recognizes the C end region of HIV-1p24
antigen, especially recognizes peptide p24bc (listed at sequence number
24) of amino acid sequence 113-303. Main recognition part of monoclonal
antibody is difference from that of polyclonal antibody and one kind
thereof recognizes the N or end peptide p24a + (amino acid sequence listed
at sequence number 28), i.e., amino acid sequence 1-112 of HIV-1p24
antigen, and produces N end peptide as immunogen. The other kind thereof
recognizes an intermediate part or peptide p24ab (listed at sequence
number 20), i.e., amino acid sequence 22-212, and produces peptide at the
intermediate part as immunogen.
COPYRIGHT: (C)2001,JPO

L4 ANSWER 14 OF 14 JAPIO (C) 2003 JPO on STN
AN 2000-099771 JAPIO
TI AUTOMATIC TICKET ISSUING MACHINE SYSTEM
IN MURATA KOUKI; ***UMETANI ATSUSHI*** ; HISHIKAWA HIROYUKI
PA SHINKO ELECTRIC CO LTD
PI JP 2000099771 A 20000407 Heisei

AI JP 1998-265551 (JP10265551 Heisei) 19980918
PRAI JP 1998-265551 19980918
SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2000
AB PROBLEM TO BE SOLVED: To provide a function capable of saving the clerk's
time and labor and enabling a hall user to immediately grasp the number of
remaining seats or the like and set up a standard for purchasing admission
tickets of the same sort.
SOLUTION: Optional one of plural ticket issuing machines 5 is determined
as a master machine and remaining ticket issuing machines 5 are set as
slave machines. When the closing processing of the master machine is
executed at the time of closing processing, the master machine
simultaneously collects also the adjustment data of all the remaining
slave machines. After completing the totalization of all the machines, a
totalization slip for the master machine and all the slave machines is
printed out from the master machine. A message to be displayed on liquid
crystal display(LCD) devices 6 and an intra-hall display device 8 is
loaded from a floppy disk 7 to the machines 5. Variable display data such
as the number of remaining seats are informed from a management device 1
to the machines 5 at real time and the number of remaining seats or the
like is displayed on the LCD devices 6 on the machines 5 and the intra-
hall display device 8 in real time.
COPYRIGHT: (C)2000,JPO

=> e miyakoshi hideo/au

E1 1 MIYAKOSHI HIDEKATSU/AU
E2 1 MIYAKOSHI HIDEKI/AU
E3 28 --> MIYAKOSHI HIDEO/AU
E4 1 MIYAKOSHI HIDETOSHI/AU
E5 30 MIYAKOSHI HIROAKI/AU
E6 1 MIYAKOSHI HIROBUMI/AU
E7 40 MIYAKOSHI HIROCHIKA/AU
E8 1 MIYAKOSHI HIROHARU/AU
E9 1 MIYAKOSHI HIROKI/AU
E10 5 MIYAKOSHI HIROMICHI/AU
E11 7 MIYAKOSHI HIRONORI/AU
E12 21 MIYAKOSHI HIROSHI/AU

=> s e3

L5 28 "MIYAKOSHI HIDEO"/AU

=> dup rem l5

PROCESSING COMPLETED FOR L5

L6 24 DUP REM L5 (4 DUPLICATES REMOVED)

=> d bib ab 1-

YOU HAVE REQUESTED DATA FROM 24 ANSWERS - CONTINUE? Y/(N):y

L6 ANSWER 1 OF 24 USPATFULL on STN

AN 2003:213736 USPATFULL

TI Anti-abnormal type prion monoclonal antibody, process for producing the
same, and immunoassay using the same

IN Kurano, Yoshihiro, Chuo-ku, JAPAN

Umetani, Atsushi, Chuo-ku, JAPAN

Miyakoshi, Hideo, Chuo-ku, JAPAN

Yanagiya, Takayuki, Chuo-ku, JAPAN

PI US 2003148374 A1 20030807

AI US 2001-5120 A1 20011207 (10)

DT Utility

FS APPLICATION

LREP BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 567

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A monoclonal antibody which enables to distinguish the abnormal type prion from the normal type prion, as well as production process thereof, is disclosed. The anti-abnormal type prion monoclonal antibody of the invention reacts with abnormal type prion by antigen-antibody reaction but does not substantially react with normal type prion by antigen-antibody reaction. The anti-abnormal type prion monoclonal antibody of the invention may be obtained by immunizing an animal with an immunogen including a peptide containing a plurality of regions in the abnormal type prion, which regions are discontinuous each other in primary amino acid sequence of the abnormal type prion.

L6 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2002:446128 CAPLUS

DN 137:19391

TI Monoclonal antibody for distinguishing abnormal type prion from normal type prion and immunoassay kit

IN Kurano, Yoshihiro; Umetani, Atsushi; ***Miyakoshi, Hideo*** ; Yanagiya, Takayuki

PA Fujirebio Inc., Japan

SO Eur. Pat. Appl., 12 pp.

CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1213301	A2	20020612	EP 2001-310310	20011210
EP 1213301	A3	20020619		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
WO 2002046236	A1	20020613	WO 2001-JP10721	20011207
W: AE, AG, AL, AM, AT, AZ, BA, BB, BG, BR, BY, BZ, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001097138	A5	20020711	AU 2001-97138	20011207
US 2003148374	A1	20030807	US 2001-5120	20011207
NZ 515982	A	20030926	NZ 2001-515982	20011207

PRAI JP 2000-374145 A 20001208

AB A monoclonal antibody which enables to distinguish the abnormal type prion from the normal type prion, as well as prodn. process thereof, is disclosed. The anti-abnormal type prion monoclonal antibody of the invention reacts with abnormal type prion by antigen-antibody reaction but does not substantially react with normal type prion by antigen-antibody reaction. The anti-abnormal type prion monoclonal antibody of the invention may be obtained by immunizing an animal with an immunogen including a peptide contg. a plurality of regions in the abnormal type prion, which regions are discontinuous each other in primary amino acid sequence of the abnormal type prion.

L6 ANSWER 3 OF 24 USPATFULL on STN

AN 96:12871 USPATFULL

TI Supplementary therapeutic agents for the treatment of immunodeficiency syndrome

IN Aoki, Tadao, Nigata, Japan

Miyakoshi, Hideo, Hachiohji, Japan

PA Ajinomoto Co., Inc., Tokyo, Japan (non-U.S. corporation)

PI US 5491150 19960213

AI US 1994-187017 19940127 (8)

PRAI JP 1993-29668 19930127

JP 1993-346875 19931227

DT Utility

FS Granted

EXNAM Primary Examiner: Prescott, Arthur C.

LREP Oblon, Spivak, McClelland, Maier, & Neustadt

CLMN Number of Claims: 10

ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 233

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A supplementary therapeutic agent for the treatment of immunodeficiency syndrome with reduced NK (natural killer) activity and an immunopotentiator preparation containing it are provided.

A supplementary therapeutic agent for immunopotentialization which comprises L-cysteine, L-cystine, or L-glutamine, or salts thereof and is used in combination with an immunopotentiator such as lentinan, OK-432, sizofiran or the like, and an immunopotentiator preparation containing the agent. This combination of agents is useful as a supplementary therapeutic agent for the treatment of an immunodeficiency, such as low NK activity syndrome, chronic fatigue syndrome, acquired immunodeficiency syndrome, or congenital immunodeficiency syndromes.

L6 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1996:91099 CAPLUS

DN 124:211680

TI Elimination or inactivation of viruses in preparation procedure of immunoglobulin products

AU Hamakado, Toshinari; Mikami, Masakazu; ***Miyakoshi, Hideo*** ; Mizukoshi, Mikio; Sato, Yoshio; Suzuki, Toyohiko; Minamishima, Yoichi

CS Fujirebio Inc., Tokyo, 163-07, Japan

SO Iyakuin Kenkyu (1995), 26(12), 975-80

CODEN: IYKEDH; ISSN: 0287-0894

PB Nippon Koteisho Kyokai

DT Journal

LA Japanese

AB To demonstrate that Ig products are free from contamination by hepatitis C virus (HCV), the authors examd. the efficiency of elimination or inactivation of Sindbis virus (SINV) and bovine diarrhea virus (BDV) as HCV models during purifn. procedures of Ig products (Globulin-N and Globulin V) from partially purified Cohn ethanol fraction by treatment with polyethylene glycol (PEG) or pepsin. The human immunodeficiency virus 1 (HIV-1) was also used as another type of RNA virus in this study. When these viruses were spiked at each step of the Ig purifn. procedure, including the treatment with PEG or pepsin, they were mostly eliminated or inactivated. Moreover, a complete elimination of viruses was obsd. in the filtration process with the virus removal membrane "Planova 35". Thus, by a combination of the conventional process and the filtration process with the virus removal membrane, highly effective elimination or inactivation of possibly contaminating viruses is achievable during the manufg. process of Ig products.

L6 ANSWER 5 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 1995:345776 BIOSIS
 DN PREV199598360076
 TI Development and usefulness of the gelatin-particle-agglutination test for titration of antibodies against diphtheria, pertussis and tetanus toxins.
 AU Miyamura, Kikuko [Reprint author]; Sadahiro, Seiji; Konda, Toshifumi; Takahashi, Motohide; Fujino, Ryuichi; Nishimura, Yuko; ***Miyakoshi,***
 *** Hideo*** ; Horiuchi, Kiyoshi; Furuya, Youichi; Kubota, Tsutomu; Watanabe, Haruo; Inouye, Sakae; Yamazaki, Shudo
 CS Dep. Epidemiol., Natl. Inst. Health, 1-23-1, Toyama, Shinjuku-ku, Tokyo 162, Japan
 SO Japanese Journal of Medical Science and Biology, (1995) Vol. 48, No. 1, pp. 49-59.
 CODEN: JJMCAQ. ISSN: 0021-5112.

DT Article
 LA English
 ED Entered STN: 10 Aug 1995
 Last Updated on STN: 10 Aug 1995

AB The gelatin-particle-agglutination (PA) test for titrating antibodies against diphtheria, pertussis and tetanus toxins was developed and used for assaying 65 sera from healthy children to assess the antitoxin acquisition in relation to the administration of adsorbed diphtheria-purified pertussis-tetanus (DPT) combined vaccine. The antitoxin titers obtained by the PA test and the conventional methods were correlated well; the correlation coefficient of the diphtheria antitoxin titers between the PA test and the cell culture method was 0.908, that of the tetanus antitoxin titers between the PA test and the passive hemagglutination test 0.968, and that of anti-pertussis toxin titers between the PA test and polystyrene-ball ELISA 0.885. The PA test was shown to be useful in both developed and developing countries, since it is simple to perform, sensitive and specific, and the three antitoxins can be titrated by the same procedure.

L6 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1994:549057 CAPLUS
 DN 121:149057
 TI L-cysteine, L-cystine or L-glutamine as a supplementary therapeutic agent for the treatment of immunodeficiency syndrome
 IN Aoki, Tadao; ***Miyakoshi, Hideo***
 PA Ajinomoto Co., Inc., Japan
 SO Eur. Pat. Appl., 8 pp.
 CODEN: EPXXDW

DT Patent
 LA English
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 609701	A1	19940810	EP 1994-100732	19940119
R: AT, BE, CH, DE, DK, ES, FR, GB, IE, IT, LI, NL, SE				
JP 06279276	A2	19941004	JP 1993-346875	19931227
JP 2947044	B2	19990913		
US 5491150	A	19960213	US 1994-187017	19940127
PRAI JP 1993-29668		19930127		
JP 1993-346875		19931227		

AB A supplementary therapeutic agent for the treatment of immunodeficiency syndrome with reduced natural killer activity and an immunostimulant prepn. contg. it are provided. A supplementary therapeutic agent for immunostimulation comprises L-cysteine, L-cystine or L-glutamine or a salt thereof which is used in combination with an immunostimulant such as lentinan, OK-432, sizofiran or the like. A male patient suffering from chronic fatigue syndrome with low natural killer activity of 18.7% who was receiving lentinan (I) was treated with i.v. infusion and oral capsules

contg. L-cystine (II) to show a gradual improvement of the clin. condition and increase in natural killer activity to 40.9% a mo after the combined use of I and II.

L6 ANSWER 7 OF 24 JAPIO (C) 2003 JPO on STN
AN 1994-279276 JAPIO
TI AUXILIARY THERAPEUTIC AGENT FOR TREATING IMMUNODEFICIENCY SYNDROME
IN AOKI TADAO; ***MIYAKOSHI HIDEO***
PA AJINOMOTO CO INC
PI JP 06279276 A 19941004 Heisei
AI JP 1993-346875 (JP05346875 Heisei) 19931227
PRAI JP 1993-29668 19930127
SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1994
AB PURPOSE: To obtain an auxiliary therapeutic agent for treating immunodeficiency and an immunopotentiator containing the auxiliary therapeutic agent.
CONSTITUTION: The auxiliary therapeutic agent for immunopotentiator comprising an auxiliary therapeutic agent for immune enhancing agent, e.g. L-cysteine, L-cystine or L-glutamine or its salt which is used together with an immunopotentiator, e.g. renchinan, OK-432 or sizofiran, or the immunopotentiator containing the auxiliary therapeutic agent. By combinedly using this immunopotentiator and this auxiliary therapeutic agent, NK-activity is raised and simultaneously clinical disorder can also be improved.
COPYRIGHT: (C)1994,JPO

L6 ANSWER 8 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1994:62258 BIOSIS
DN PREV199497075258
TI Low NK syndrome and its relationship to chronic fatigue syndrome.
AU Aoki, Tadao [Reprint author]; ***Miyakoshi, Hideo*** ; Usuda, Yoshimaru; Herberman, Ronald B.
CS Lab. Med. Sci., Ajinomoto Co. Inc., c/o Advanced BioScience Lab. Inc., 5510 Nicholson Lane, Kensington, MD 20895, USA
SO Clinical Immunology and Immunopathology, (1993) Vol. 69, No. 3, pp. 253-265.
CODEN: CLIIAT. ISSN: 0090-1229.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 9 Feb 1994
Last Updated on STN: 9 Feb 1994

L6 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
AN 1992:424680 CAPLUS
DN 117:24680
TI Method and reagents for detecting HTLV-I virus antibody in blood by electrophoresis-immunoassay
IN ***Miyakoshi, Hideo*** ; Sugimoto, Masazumi; Honda, Hideo
PA Fujirebio K. K., Japan
SO Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI JP 04086558 A2 19920319 JP 1990-201860 19900730
JP 2971537 B2 19991108
PRAI JP 1990-201860 19900730
AB The title method involves (1) (polyacrylamide) gel electrophoresis of

human T-lymphotrophic virus type I (HTLV-I) antigen mixt. to sep. HTLV-I gene env antigen; (2) gel electrophoresis of the sepd. HTLV-I gene env antigen; (3) transfer of the HTLV-I gene env antigen to a carrier (nitrocellulose membrane); (4) reaction of a test sample (contg. antibodies) with the electrophoresed antigen; and (5) detecting bound antibody using, e.g., biotinylated anti-human antibody and peroxidase-labeled avidin. A reagent contg. HTLV-I virus antigen for the anal. also is claimed. The method is specific and clear (i.e. no overlapped bands).

L6 ANSWER 10 OF 24 JAPIO (C) 2003 JPO on STN
AN 1992-198865 JAPIO
TI IMMUNE MEASUREMENT
IN TAMAGAWA KANNA; ***MIYAKOSHI HIDEO***
PA FUJIREBIO INC
PI JP 04198865 A 19920720 Heisei
AI JP 1990-332224 (JP02332224 Heisei) 19901129
PRAI JP 1990-332224 19901129
SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1992
AB PURPOSE: To enable detection of an antibody with high reproducibility by incorporating a process wherein a ferritin-labeled antibody forms color in reaction with hinokitiol to eliminate variations in results as caused by a measuring person or the like with a handy operation.
CONSTITUTION: A ferritin-labelled antibody can be made by a method used in a ferritin antibody method and that available commercially is usable. A reaction between the antibody and a hinokitiol aqueous solution is accomplished for about 1-120 minute at a room temperature. A sample can be used without dilution and an antigen to be measured is not limited. For example, a ferritin- labelled anti-human IgG (concentration of protein of 6mg/ml) diluted by 2<SP>n</SP> times is put into a well of a microtiter plate and 0.025 ml of a 0.5% hinokitiol aqueous solution is put into each well to cause a reaction for one minute at the room temperature. This enables observation of a color of red formed at a concentration exceeding 15 μg/ml (400 fold dilution) in the concentration of the antibody.
COPYRIGHT: (C)1992,JPO&Japio

L6 ANSWER 11 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2
AN 1993:52690 BIOSIS
DN PREV199395028992
TI Improvement of simultaneous detection of antibodies to gag and envelope antigens of human T-lymphotropic virus type I by Western immunoblot assay.
AU ***Miyakoshi, Hideo*** [Reprint author]; Sugimoto, Masazumi; Igarashi, Hiroyoshi; Honda, Hideo; Fujino, Ryuichi; Mizukoshi, Mikio
CS Diagnostics Res. Lab., Fujirebio Inc., 51 Komiya cho, Hachioji, Tokyo 192, Japan
SO Journal of Clinical Microbiology, (1992) Vol. 30, No. 10, pp. 2555-2559.
CODEN: JCMIDW. ISSN: 0095-1137.
DT Article
LA English
ED Entered STN: 13 Jan 1993
Last Updated on STN: 13 Jan 1993
AB To determine seropositivity for human T-lymphotropic virus type I (HTLV-I), we attempted to improve the detection system that uses antibody to HTLV-I Env in Western immunoblotting (WB) by adding an envelope glycoprotein (gp46) purified from the culture fluid of HTLV-I producing cells by immunoaffinity chromatography and gel chromatography. In this WB, 177 of 179 serum samples showing seropositivity in an indirect immunofluorescence assay showed positive reactions to the gp46 envelope antigen as well as to p19, p24, and p53 Gag antigens. The remaining two samples showed negative reactions to p24. False-positive results were not

found for 533 indirect immunofluorescence assay-negative serum samples, although one band to p19 or p24 was observed in 46 of the 533 samples. These 46 samples did not react to p53 and gp46, suggesting that these samples belonged to the indeterminate group in accordance with the criteria proposed by the World Health Organization. Therefore, this improved WB can be used for the confirmation of seropositivity.

L6 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1991:469624 CAPLUS

DN 115:69624

TI Improvement of gelatin particle agglutination test for detection of anti-HTLV-I antibody

AU Fujino, Ryuichi; Kawato, Katsuhito; Ikeda, Mikio; ***Miyakoshi, Hideo*** ; Mizukoshi, Mikio; Imai, Joko

CS Diagn. Res. Lab., Fujirebio INC., Hachioji, 192, Japan

SO Japanese Journal of Cancer Research (1991), 82(4), 367-70

CODEN: JJCREP; ISSN: 0910-5050

DT Journal

LA English

AB Partial modifications of antigen components were made to improve the gelatin particle agglutination (PA) test for the detection of antibodies against human T cell leukemia virus type-I. Envelope glycoproteins prep'd. by lentil lectin affinity chromatog. were further added to the purified viral antigens to be coated on the gelatin particles. Comparative studies with a conventional PA test kit and indirect immunofluorescence assay showed that the specificity and sensitivity of the new PA test were increased and that abnormal agglutination such as the prozone phenomenon was abolished by this improvement.

L6 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 3

AN 1991:22463 CAPLUS

DN 114:22463

TI Manufacture of lymphocyte stimulant MP-A with Staphylococcus aureus

IN Koyamaishi, Yoshihiro; Mizukoshi, Mikio; ***Miyakoshi, Hideo*** ; Sugimoto, Masazumi

PA Fujirebio, Inc., Japan

SO Jpn. Kokai Tokkyo Koho, 7 pp.

CODEN: JKXXAF

DT Patent

LA Japanese

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI JP 02150291	A2	19900608	JP 1988-300978	19881130
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PRAI JP 1988-300978		19881130		
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AB MP-A, a 104-dalton (by SDS-PAGE) lymphocyte-stimulating substance having mitogenic and cytotoxic activities and capable of inducing interleukin-2 (IL-2), interferon- γ (INF- γ), and IgG prodn., is manuf'd. from Staphylococcus aureus. The cell homogenate of S. aureus from an 8-L culture was used to recover MP-A (1.7 OD280; 2 mL) by (NH₄)₂SO₄-pptn., chromatog., and chromatofocusing (pH 4.7-4.5).

L6 ANSWER 14 OF 24 JAPIO (C) 2003 JPO on STN

AN 1990-016973 JAPIO

TI HUMAN NORMAL OSTEOBLASTIC STRAIN AND METHOD FOR OBTAINING SAID STRAIN

IN ***MIYAKOSHI HIDEO*** ; TANIZAWA TATSUHIKO; AOKI TADAO

PA FUJIREBIO INC

PI JP 02016973 A 19900119 Heisei

AI JP 1988-165851 (JP63165851 Showa) 19880705

PRAI JP 1988-165851 19880705

SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1990

AB PURPOSE: To apply a human normal osteoblastic strain to osteoporosis, renal osteodystrophia, fracture, etc., of the aged with deteriorated osteogenetic ability and enable promotion of osteogenesis by obtaining the human osteoblastic strain from a human bone tissue.

CONSTITUTION: A human bone tissue, such as infant long bone, is taken out and treated with a collagenase solution to remove fibroblasts and provide human osteoblasts. A human bone tissue is then cultured in a low-calcium culture solution or further culture solution used for normal tissue culture, such as BGJb or Eagle's minimum essential medium (MEM). Cell establishment (cloning) derived from one cell is then carried out to confirm that the cells are osteoblasts by positive to staining with an alkaline phosphatase. The positive ratio is enhanced from conventional 10-30% to 50%. Thereby, osteogenesis can be accelerated by application to osteoporosis, renal osteodystrophia or fracture, etc., of the aged with deteriorated osteogenesis. In the case of especially the aged, the method is advantageous in that dementia of the bedridden aged due to fracture can be prevented.

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L6 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 4

AN 1984:137244 CAPLUS

DN 100:137244

TI Diagnostic method for immune disorders

IN Aoki, Tadao; ***Miyakoshi, Hideo*** ; Mizukoshi, Mikio

PA Fujirebio, Inc., Japan

SO U.S., 2 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 4426454	A	19840117	US 1981-246544	19810323
JP 56135159	A2	19811022	JP 1980-37504	19800326
JP 62023824	B4	19870525		
PRAI JP 1980-37504		19800326		

AB A method is described for diagnosis of immune disorders in humans, which involves detg. the Ig prodn. and the DNA formation by peripheral blood lymphocytes (PBL) which have been stimulated by disintegrated cells or the culture fluid of Staphylococcus cells. The disintegrated cells or culture fluid act on B-lymphocytes mitogenically, thus stimulating formation of Igs. For example, S. aureus was cultured, and then lysed. PBL from healthy humans and from patients with immune disorders were incubated with the lysate for 168 h at 37.degree.. Ig (IgM or IgG) formation by PBL from patients with immune disorders was decreased to 33-25% of that formed by PBL from healthy humans, and DNA formation, as detd. by incorporation of [3H]thymidine, was decreased 50-33% in immune disorders.

L6 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1984:543735 CAPLUS

DN 101:143735

TI Acting mechanisms of Lentinan in human. II. Enhancement of non-specific cell-mediated cytotoxicity as an interferon inducer

AU ***Miyakoshi, Hideo*** ; Aoki, Tadao; Mizukoshi, Mikio

CS Shinrakuen Hosp., Niigata, 950-21, Japan

SO International Journal of Immunopharmacology (1984), 6(4), 373-9

CODEN: IJIMDS; ISSN: 0192-0561

DT Journal

LA English

AB The immunopotentiator Lentinan [37339-90-5] augmented the cell-mediated cytotoxicity in humans. The activation of killer T cells by the mixed

lymphocyte culture was accelerated only when responder cells were mixed with both a suboptimum no. of stimulator cells and Lentinan. The interferon level in the peripheral blood circulation of cancer patients was elevated in 12 h following Lentinan administration, and natural killer activity of peripheral mononuclear cells was enhanced in 48 h. These data indicate that Lentinan inhibits cancer by favorably affecting the host defense mechanisms of man.

L6 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1984:543781 CAPLUS

DN 101:143781

TI Acting mechanisms of Lentinan in human. I. Augmentation of DNA synthesis and immunoglobulin production of peripheral mononuclear cells

AU ***Miyakoshi, Hideo*** ; Aoki, Tadao

CS Shinrakuen Hosp., Niigata, 950-21, Japan

SO International Journal of Immunopharmacology (1984), 6(4), 365-71

CODEN: IJIMDS; ISSN: 0192-0561

DT Journal

LA English

AB The immunopotentiating mechanisms of Lentinan [37339-90-5] were investigated in human systems. Augmentation of DNA synthesis of peripheral mononuclear cells (PMNC) occurred both in vitro and in vivo by adding or injecting Lentinan, for which the coexistence of T cells, B cells and adherent cells (mainly monocytes) was essential. No addnl. mitogenic effect of Lentinan was obsd. when PMNC were incubated with both Lentinan and other mitogens. In vitro prodn. of Ig by PMNC induced with pokeweed mitogen was enhanced through the inhibition of suppressor T cell activity by Lentinan.

L6 ANSWER 18 OF 24 USPATFULL on STN

AN 82:36468 USPATFULL

TI Method for suppressing abnormal rise in immunological function and agent useful therefor

IN Aoki, Takao, Niigata, Japan

Miyakoshi, Hideo , Niigata, Japan

Hirasawa, Yoshihei, Niigata, Japan

Nishii, Yasuo, Tokyo, Japan

PA Chugai Seiyaku Kabushiki Kaisha, Tokyo, Japan (non-U.S. corporation)

PI US 4341774 19820727

AI US 1980-176642 19800811 (6)

PRAI JP 1979-101211 19790810

DT Utility

FS Granted

EXNAM Primary Examiner: Roberts, Elbert L.

LREP Browdy and Neimark

CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 208

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for suppressing abnormal rise in immunological function which often causes various types of autoimmune diseases, and an agent useful therefor are disclosed. The method is carried out by administering cholecalciferol or its derivative to patients suffering from abnormal rise in immunological function. The agent contains the above compound as active ingredient and is useful not only to treat and/or prevent the abnormal rise in immunological function but also to suppress graft rejection.

L6 ANSWER 19 OF 24 USPATFULL on STN

AN 82:35211 USPATFULL

TI Method for inhibiting the lowering of immunological function and agent therefor

IN Aoki, Tadao, Niigata, Japan

Miyakoshi, Hideo, Niigata, Japan

Hirasawa, Yoshihei, Niigata, Japan

Nishii, Yasuo, Tokyo, Japan

PA Chugai Seiyaku Kabushiki Kaisha, Tokyo, Japan (non-U.S. corporation)

PI US 4340604 19820720

AI US 1980-176641 19800811 (6)

PRAI JP 1979-101210 19790810

DT Utility

FS Granted

EXNAM Primary Examiner: Roberts, Elbert L.

LREP Browdy and Neimark

CLMN Number of Claims: 3

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 139

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for inhibiting the lowering of immunological function of patients who are suffering from serious renal disorder such as chronic renal failure or uremia which comprises administering 1.alpha.-hydroxycholecalciferol to the patients is disclosed. An agent useful in the practice of the method is also disclosed.

L6 ANSWER 20 OF 24 JAPIO (C) 2003 JPO on STN

AN 1981-135159 JAPIO

TI IMMUNOLOGICAL DIAGNOSIS METHOD

IN AOKI TADAO; ***MIYAKOSHI HIDEO***; MIZUKOSHI MIKIO

PA FUJIREBIO INC

PI JP 56135159 A 19811022 Showa

AI JP 1980-37504 (JP55037504 Showa) 19800326

PRAI JP 1980-37504 19800326

SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1981

AB PURPOSE: To perform an accurate diagnosis of disease accompanied by the functional abnormality of lymphocyte originating from marrow by measuring the globulin production capacity of lymphocyte originating from marrow using a component obtained through the crushing of yellow staphilococcus or using the culture filtrate of this micrococcus.

CONSTITUTION: After the culturing of yellow staphilococcus in a nutritious culture bed, either a component obtained through the crushing of a micrococcus by means of an ultrasonic wave, etc. or a culture filtrate obtained through the filtration of a culture solution is used. Then the immunized globulin production capacity of lymphocyte originating from marrow is measured by the dual antibody radiation immunological test method, etc. A patient having an abnormal immunity shows an immunized globulin production capacity lower than a healthy person by approximately $1/3 \sim 1/4$. Through this measurement, the deterioration of the function of lymphocyte originating from marrow can be diagnosed with high precision.

COPYRIGHT: (C)1981,JPO&Japio

L6 ANSWER 21 OF 24 JAPIO (C) 2003 JPO on STN

AN 1981-026820 JAPIO

TI IMMUNOSUPPRESSING AGENT

IN AOKI TADAO; ***MIYAKOSHI HIDEO***; HIRASAWA YOSHIHEI; NISHII YASUHO

PA CHUGAI PHARMACEUT CO LTD

PI JP 56026820 A 19810316 Showa

AI JP 1979-101211 (JP54101211 Showa) 19790810

PRAI JP 1979-101211 19790810

SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1981

AB PURPOSE: To provide an immunosuppressing agent containing cholecalciferol or its derivative as an effective component, and effective to the immunological hyperergasia such as chronic thyroaderitis, autoimmune hemolytic anemia, etc.

CONSTITUTION: An agent containing as an effective component, known cholecalciferol or its derivative (e.g. 1 α -hydroxycholecalciferol) found in tuna-liver oil or synthesized by the UV-irradiation of 7-dehydrocholesterin. It has been found that the compound is effective not only to control the calcium metabolism but also to suppress the immunity of the body. The necessary dose is very small, and the blood concentration of 0.01mg/ml \sim 1 μ g/ml is sufficient. It is preferable to be administered as a soft capsule. The agent has improved effectiveness and reduced side effects.

COPYRIGHT: (C)1981,JPO&Japio

L6 ANSWER 22 OF 24 JAPIO (C) 2003 JPO on STN

AN 1981-026819 JAPIO

TI PREVENTIVE FOR HYPOIMMUNITY

IN AOKI TADAO; ***MIYAKOSHI HIDEO*** ; HIRASAWA YOSHIHEI; NISHII YASUHO

PA CHUGAI PHARMACEUT CO LTD

PI JP 56026819 A 19810316 Showa

AI JP 1979-101210 (JP54101210 Showa) 19790810

PRAI JP 1979-101210 19790810

SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1981

AB PURPOSE: To provide a preventive for the hyp immunity of hemodialysis patients, by the use of 1 α -hydroxycholecalciferol as an effective component.

CONSTITUTION: Preventive for hyp immunity of hemodialysis patients is prepared by using, as an effective component, 1 α -hydroxycholecalciferol (1 α -OH-D \rightarrow 3</SB>) which is an active vitamin D \rightarrow 3</SB>. It has been found that the hemodialysis patient suffers from hyp immunity after the hemodialysis by the accumulation of unknown immunosuppressing materials in the blood. When 1 α -OH-D \rightarrow 3</SB> is administered to the patient for the purpose of controlling calcium metabolism, the immunity of the patient does not decrease and the infectious diseases are prevented. Usually, 0.25 \sim 10 μ g of the compound is administered to an adult per day. The above-mentioned immunosuppressing material has a molecular weight of about 50,000 or more and a poor thermal stability.

COPYRIGHT: (C)1981,JPO&Japio

L6 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1982:67127 CAPLUS

DN 96:67127

TI Mitogenic substances in staphage lysate

AU ***Miyakoshi, Hideo*** ; Aoki, Tadao; Mizukoshi, Mikio

CS Res. Div., Shinrakuen Hosp., Niigata, 950-21, Japan

SO Biomedical Research (1981), 2(6), 629-38

CODEN: BRESDD; ISSN: 0388-6107

DT Journal

LA English

AB The biol. characteristics of staphage lysate (SPL) were immunol. examd. and the mitogenic substance in SPL was isolated. SPL is a potent mitogen for the peripheral blood lymphocytes (PBL) of most healthy human donors. Viable staphylococcus bacteriophage used to lyse Staphylococcus aureus is not responsible for this mitogenic activity nor is it necessary for the lysis of S. aureus. SPL contains protein A which does not contribute to the mitogenic activity. The following conclusions regarding SPL have been reached. The mol. wt. of the mitogenic substance is approx. 25,000 daltons. SPL is as strong a mitogen as phytohemagglutinin, concanavalin A, and pokeweed mitogen (PWM). It enhances the DNA synthesis of both T

cells and non-T cells; the proliferation of T cells takes place only in the presence of adherent cells and the proliferation of non-T cells requires the helper function of T cells. Like PWM, SPL augments IgM as well as IgG syntheses by PBL. Therefore, SPL is a useful mitogen for the in vitro study of cell-mediated immunity.

L6 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1981:207041 CAPLUS
DN 94:207041
TI Staphage lysate and lentinan as immunomodulators and/or immunopotentiators in clinical and experimental systems
AU Aoki, Tadao; ***Miyakoshi, Hideo*** ; Horikawa, Yoh; Usuda, Yoshimaru
CS Shinrakuen Hosp., Niigatashi, 950-21, Japan
SO Progress in Cancer Research and Therapy (1981), 16(Augmenting Agents Cancer Ther.), 101-12
CODEN: PCRTDK; ISSN: 0145-3726
DT Journal
LA English
AB Exptl. results are described on the properties and activities of staphage lysate (components of Staphylococcus aureus lysed by a polyvalent bacteriophage) and lentinan (a polysaccharide from Lentinus edodes). The data report toxicities, biol. activities (Ig- and interferon-inducing, etc.), therapeutic activities (mainly antitumor), and mechanisms of action. Their immunol. properties are discussed in the light of these findings.

=> s (bp-7808)
L7 1 (BP-7808)

=> d bib ab kwic

L7 ANSWER 1 OF 1 USPATFULL on STN
AN 2003:213736 USPATFULL
TI Anti-abnormal type prion monoclonal antibody, process for producing the same, and immunoassay using the same
IN Kurano, Yoshihiro, Chuo-ku, JAPAN
Umetani, Atsushi, Chuo-ku, JAPAN
Miyakoshi, Hideo, Chuo-ku, JAPAN
Yanagiya, Takayuki, Chuo-ku, JAPAN
PI US 2003148374 A1 20030807
AI US 2001-5120 A1 20011207 (10)
DT Utility
FS APPLICATION
LREP BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 567
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A monoclonal antibody which enables to distinguish the abnormal type prion from the normal type prion, as well as production process thereof, is disclosed. The anti-abnormal type prion monoclonal antibody of the invention reacts with abnormal type prion by antigen-antibody reaction but does not substantially react with normal type prion by antigen-antibody reaction. The anti-abnormal type prion monoclonal antibody of the invention may be obtained by immunizing an animal with an immunogen including a peptide containing a plurality of regions in the abnormal type prion, which regions are discontinuous each other in primary amino acid sequence of the abnormal type prion.
DETD . . . to international deposition under the Budapest Treaty on Nov.

21, 2001, the accession No. of the international deposition being FERM
BP - ***7808*** .

DETD . . . been deposited with National Institute of Advanced Industrial
Science and Technology under the Budapest Treaty under an accession No.
FERM ***BP*** - ***7808*** , as mentioned above.

CLM What is claimed is:

5. A monoclonal antibody or the antigen-binding fragment thereof, which
is produced by hybridoma EBEB4C3Ebb (FERM ***BP*** - ***7808***).

=> s (p-18013)

L8 1 (P-18013)

=> d bib ab kwic 1-

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y

L8 ANSWER 1 OF 1 USPATFULL on STN

AN 2003:213736 USPATFULL

TI Anti-abnormal type prion monoclonal antibody, process for producing the
same, and immunoassay using the same

IN Kurano, Yoshihiro, Chuo-ku, JAPAN

Umetani, Atsushi, Chuo-ku, JAPAN

Miyakoshi, Hideo, Chuo-ku, JAPAN

Yanagiya, Takayuki, Chuo-ku, JAPAN

PI US 2003148374 A1 20030807

AI US 2001-5120 A1 20011207 (10)

DT Utility

FS APPLICATION

LREP BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 567

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A monoclonal antibody which enables to distinguish the abnormal type
prion from the normal type prion, as well as production process thereof,
is disclosed. The anti-abnormal type prion monoclonal antibody of the
invention reacts with abnormal type prion by antigen-antibody reaction
but does not substantially react with normal type prion by
antigen-antibody reaction. The anti-abnormal type prion monoclonal
antibody of the invention may be obtained by immunizing an animal with
an immunogen including a peptide containing a plurality of regions in
the abnormal type prion, which regions are discontinuous each other in
primary amino acid sequence of the abnormal type prion.

DETD . . . Tsukuba Central 6, 1-1, Higashi 1-chome, Tsukuba-shi,
Ibaraki-ken 305-8566 Japan as of Sep. 1, 2000 under the accession No.
FERM ***P*** - ***18013*** (original deposition), and the
deposition was converted to international deposition under the Budapest
Treaty on Nov. 21, 2001, the accession. . .

=> s hybridoma and EBEB4C3Ebb

L9 1 HYBRIDOMA AND EBEB4C3EBB

=> d bib ab kwic

L9 ANSWER 1 OF 1 USPATFULL on STN

AN 2003:213736 USPATFULL

TI Anti-abnormal type prion monoclonal antibody, process for producing the
same, and immunoassay using the same

IN Kurano, Yoshihiro, Chuo-ku, JAPAN
Umetani, Atsushi, Chuo-ku, JAPAN
Miyakoshi, Hideo, Chuo-ku, JAPAN
Yanagiya, Takayuki, Chuo-ku, JAPAN

PI US 2003148374 A1 20030807

AI US 2001-5120 A1 20011207 (10)

DT Utility

FS APPLICATION

LREP BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747

CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 567

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A monoclonal antibody which enables to distinguish the abnormal type prion from the normal type prion, as well as production process thereof, is disclosed. The anti-abnormal type prion monoclonal antibody of the invention reacts with abnormal type prion by antigen-antibody reaction but does not substantially react with normal type prion by antigen-antibody reaction. The anti-abnormal type prion monoclonal antibody of the invention may be obtained by immunizing an animal with an immunogen including a peptide containing a plurality of regions in the abnormal type prion, which regions are discontinuous each other in primary amino acid sequence of the abnormal type prion.

SUMM . . . substantially react with normal type prion by antigen-antibody reaction, or an antigen-binding fragment thereof. The present invention also provides a ***hybridoma*** which produces the monoclonal antibody according to the present invention. The present invention further provides a method for measuring abnormal. . . amino acid sequence of said abnormal type prion; preparing hybridomas originated from antibody-producing cells of the immunized animal; screening a ***hybridoma*** which produces an anti-abnormal type prion monoclonal antibody which reacts with the abnormal type prion but does not substantially react with the normal type prion by antigen-antibody reaction; and recovering said anti-abnormal type prion monoclonal antibody from the ***hybridoma*** selected by the screening. The present invention still further provides an immunogen used in the above-mentioned process for producing the. . .

DETD . . . such as the acid-autoclave treatment. Examples of such an anti-abnormal type prion monoclonal antibody include the monoclonal antibody produced by ***hybridoma*** ***EBEB4C3Ebb***. The ***hybridoma*** ***EBEB4C3Ebb*** has been deposited with National Institute of Advanced Industrial Science and Technology (formerly National Institute of Bioscience and Human-Technology, Agency. . .

DETD . . . comprises the E2 region, which peptides are bound to the same KLH molecule, the monoclonal antibody produced by the above-mentioned ***hybridoma*** ***EBEB4C3Ebb*** was obtained. The above-described regions may be directly ligated or indirectly ligated by inserting one to several amino acids therebetween. . .

DETD . . . and does not substantially react with the normal type prion, and the desired monoclonal antibody is recovered from the screened ***hybridoma***. The method for preparing hybridomas by fusing antibody-producing cells such as spleen cells and lymphocytes with immortalized cells such as. . .

DETD . . . was reacted and existence of antibody-producing cell was checked based on the coloring reaction. The number of positive clones of ***hybridoma*** is shown in Table 1.

TABLE 1

Fusion Efficiency

100%

LA English

ED Entered STN: 27 Jun 2001

Last Updated on STN: 19 Feb 2002

AB The carbohydrate antigen on heparan sulfate recognized by ***monoclonal*** antibody 10E4 is uniquely codistributed with the ***abnormal*** ***prion*** protein, PrPSc, even in the earliest detectable brain lesions of scrapie-infected mice. Determining the chemical structure of 10E4 antigen is, therefore, an important aspect of structure elucidation of scrapie lesions, and a prerequisite for designing experiments to understand its role in scrapie pathogenesis. Toward this aim, we have examined preparations of heparan sulfate, with differing sulfate contents, for binding by 10E4 antibody. The highest antigenicity was observed in a preparation (HS-1) with the lowest sulfate content. HS-1 was partially depolymerized with heparin lyase III, and oligosaccharide fragments examined for 10E4 antigen expression by the neoglycolipid technology. An antigen-positive and two antigen-negative tetrasaccharides were isolated and examined by electrospray mass spectrometry. The antigen-positive tetrasaccharide sequence on heparan sulfate was thus deduced to contain a unique unsulfated motif that includes an N-unsubstituted glucosamine in the sequence, UA-GlcN-UA-GlcNAc. Antibody binding experiments with neoglycolipids prepared from a series of heparin/heparan sulfate disaccharides, and the trisaccharide derived from the antigen-positive tetrasaccharide after removal of the terminal hexuronic acid, show that both the penultimate glucosamine and the outer nonsulfated hexuronic acid are important for 10E4 antigenicity.

AB The carbohydrate antigen on heparan sulfate recognized by ***monoclonal*** antibody 10E4 is uniquely codistributed with the ***abnormal*** ***prion*** protein, PrPSc, even in the earliest detectable brain lesions of scrapie-infected mice. Determining the chemical structure of 10E4 antigen is, . . .

IT Major Concepts

Biochemistry and Molecular Biophysics; Infection; Methods and Techniques

IT Diseases

scrapie: nervous system disease, ***prion*** disease
Scrapie (MeSH)

IT Chemicals & Biochemicals

10E4 antigen; glucosamine; heparan: nonsulfated motif; heparin lyase III [EC 4.2.2.8]; IBEX Technologies, catalyst; hexuronic acid;
monoclonal antibody 10E4: Seikagaku, reagent; tetrasaccharides

L12 ANSWER 2 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 2000:115625 BIOSIS

DN PREV200000115625

TI A comparative study of immunohistochemical methods for detecting ***abnormal*** ***prion*** protein with ***monoclonal*** and polyclonal antibodies.

AU Hardt, M.; Baron, T.; Groschup, M. H. [Reprint author]

CS Federal Research Centre for Virus Diseases of Animals, 72001, Tuebingen, Germany

SO Journal of Comparative Pathology, (Jan., 2000) Vol. 122, No. 1, pp. 43-53.
print.

CODEN: JCVPAR. ISSN: 0021-9975.

DT Article

LA English

ED Entered STN: 29 Mar 2000

Last Updated on STN: 3 Jan 2002

AB Transmissible spongiform encephalopathies are associated with the accumulation of ***abnormal*** ***prion*** protein (PrPSc) in the central nervous system which can be detected immunohistochemically. Using a ***monoclonal*** antibody (L42) to an epitope on the first

alpha-helix of ruminant PrP, we compared previously reported immunohistochemical antigen unmasking and "visualization" systems. In addition, a variety of polyclonal and ***monoclonal*** antibodies to other epitopes on ruminant PrP were assessed. Antigen unmasking by hydrated autoclaving and proteinase K treatments, and antigen detection with L42 and an avidinbiotin complex system, enabled intra- and extra-neuronal PrPSc to be demonstrated in scrapie-affected sheep carrying three different PrP alleles, as well as in cases of bovine spongiform encephalopathy.

TI A comparative study of immunohistochemical methods for detecting ***abnormal*** ***prion*** protein with ***monoclonal*** and polyclonal antibodies.

AB Transmissible spongiform encephalopathies are associated with the accumulation of ***abnormal*** ***prion*** protein (PrPSc) in the central nervous system which can be detected immunohistochemically. Using a ***monoclonal*** antibody (L42) to an epitope on the first alpha-helix of ruminant PrP, we compared previously reported immunohistochemical antigen unmasking and "visualization" systems. In addition, a variety of polyclonal and ***monoclonal*** antibodies to other epitopes on ruminant PrP were assessed. Antigen unmasking by hydrated autoclaving and proteinase K treatments, and antigen. . .

IT Major Concepts

Infection; Methods and Techniques; Nervous System (Neural Coordination)

IT Diseases

'spongiform encephalopathy: nervous system disease, viral disease

Prion Diseases (MeSH)

IT Chemicals & Biochemicals

L42: ***monoclonal*** antibody; polyclonal antibodies;

prion proteins

L12 ANSWER 3 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 2000:48536 BIOSIS

DN PREV200000048536

TI New insight into ***abnormal*** ***prion*** protein using ***monoclonal*** antibodies.

AU Demart, Severine; Fournier, Jean-Guy; Creminon, Christophe; Frobert, Yveline; Lamoury, Francois; Marce, Dominique; Lasmezas, Corinne; Dormont, Dominique; Grassi, Jacques; Deslys, Jean-Philippe [Reprint author]

CS CEA, Service de Neurovirologie, DSV/DRM/CRSSA, CEA de Fontenay, 60-68, Avenue du General Leclerc, 92265, Fontenay-aux-Roses Cedex, France

SO Biochemical and Biophysical Research Communications, (Nov. 30, 1999) Vol. 265, No. 3, pp. 652-657. print.

CODEN: BBRC9. ISSN: 0006-291X.

DT Article

LA English

ED Entered STN: 3 Feb 2000

Last Updated on STN: 31 Dec 2001

AB Studies of ***abnormal*** ***prion*** protein (PrPres) are hindered by the lack of specific ***monoclonal*** antibodies (mAbs), and the relationships between PrPres, infectivity, and strain specificity in ***prion*** diseases are still subject to debate. We have studied PrPres with new mAbs produced against PrP in mice using various immunization strategies. PrPres was analyzed by Western blot with different ***prion*** strains in various hosts. Differences in the electrophoretic pattern of human PrPres revealed by these antibodies provide new insight into PrPres cleavage by proteases and interpretation of strain typing. This study confirms that the N-terminal extremity of PrPres is differentially sensitive to proteases. Conversely, the C-terminal extremity, which resists proteolysis, seems to be abnormally detectable by antibodies in ultrastructural studies. This work confirms the highly complex role of PrPres in ***prion*** diseases and provides

new tools which will be made available to facilitate progress in qualitative and quantitative studies of PrP.

TI New insight into ***abnormal*** ***prion*** protein using ***monoclonal*** antibodies.

AB Studies of ***abnormal*** ***prion*** protein (PrPres) are hindered by the lack of specific ***monoclonal*** antibodies (mAbs), and the relationships between PrPres, infectivity, and strain specificity in ***prion*** diseases are still subject to debate. We have studied PrPres with new mAbs produced against PrP in mice using various immunization strategies. PrPres was analyzed by Western blot with different ***prion*** strains in various hosts. Differences in the electrophoretic pattern of human PrPres revealed by these antibodies provide new insight into. . . seems to be abnormally detectable by antibodies in ultrastructural studies. This work confirms the highly complex role of PrPres in ***prion*** diseases and provides new tools which will be made available to facilitate progress in qualitative and quantitative studies of PrP.

IT . . .

Parts, Structures, & Systems of Organisms

brain: nervous system

IT Diseases

Creutzfeldt-Jakob disease: behavioral and mental disorders, nervous system disease, ***prion*** disease
Creutzfeldt-Jakob Syndrome (MeSH)

IT Diseases

bovine spongiform encephalopathy: nervous system disease, ***prion*** disease
Encephalopathy, Bovine Spongiform (MeSH)

IT Diseases

scrapie: nervous system disease, ***prion*** disease
Scrapie (MeSH)

IT Chemicals & Biochemicals

abnormal ***prion*** protein; ***prion*** protein;
protease

L12 ANSWER 4 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 1999:513282 BIOSIS

DN PREV199900513282

TI Oral transmission and early lymphoid tropism of chronic wasting disease
PrPres in mule deer fawns (*Odocoileus hemionus*).

AU Sigurdson, Christina J.; Williams, Elizabeth S.; Miller, Michael W.;
Spraker, Terry R.; O'Rourke, Katherine I.; Hoover, Edward A. [Reprint
author]

CS Department of Pathology, College of Veterinary Medicine and Biomedical
Sciences, Colorado State University, Fort Collins, CO, 80523-1671, USA

SO Journal of General Virology, (Oct., 1999) Vol. 80, No. 10, pp. 2757-2764.
print.

CODEN: JGVIA Y. ISSN: 0022-1317.

DT Article

LA English

ED Entered STN: 3 Dec 1999

Last Updated on STN: 3 Dec 1999

AB Mule deer fawns (*Odocoileus hemionus*) were inoculated orally with a brain homogenate prepared from mule deer with naturally occurring chronic wasting disease (CWD), a ***prion*** -induced transmissible spongiform encephalopathy. Fawns were necropsied and examined for PrPres, the ***abnormal*** ***prion*** protein isoform, at 10, 42, 53, 77, 78 and 80 days post-inoculation (p.i.) using an immunohistochemistry assay modified to enhance sensitivity. PrPres was detected in alimentary tract-associated lymphoid tissues (one or more of the following: retropharyngeal lymph node, tonsil, Peyer's patch and ileocaecal lymph

node) as early as 42 days p.i. and in all fawns examined thereafter (53 to 80 days p.i.). No PrPres staining was detected in lymphoid tissue of three control fawns receiving a control brain inoculum, nor was PrPres detectable in neural tissue of any fawn. PrPres-specific staining was markedly enhanced by sequential tissue treatment with formic acid, proteinase K and hydrated autoclaving prior to immunohistochemical staining with ***monoclonal*** antibody F89/160.1.5. These results indicate that CWD PrPres can be detected in lymphoid tissues draining the alimentary tract within a few weeks after oral exposure to infectious ***prions*** and may reflect the initial pathway of CWD infection in deer. The rapid infection of deer fawns following exposure by the most plausible natural route is consistent with the efficient horizontal transmission of CWD in nature and enables accelerated studies of transmission and pathogenesis in the native species.

AB. . . hemionus) were inoculated orally with a brain homogenate prepared from mule deer with naturally occurring chronic wasting disease (CWD), a ***prion*** -induced transmissible spongiform encephalopathy. Fawns were necropsied and examined for PrPres, the ***abnormal*** ***prion*** protein isoform, at 10, 42, 53, 77, 78 and 80 days post-inoculation (p.i.) using an immunohistochemistry assay modified to enhance. . . was markedly enhanced by sequential tissue treatment with formic acid, proteinase K and hydrated autoclaving prior to immunohistochemical staining with ***monoclonal*** antibody F89/160.1.5. These results indicate that CWD PrPres can be detected in lymphoid tissues draining the alimentary tract within a few weeks after oral exposure to infectious ***prions*** and may reflect the initial pathway of CWD infection in deer. The rapid infection of deer fawns following exposure by. . .

IT Major Concepts

Infection; Vector Biology

IT Diseases

chronic wasting disease: ***prion*** disease

Wasting Syndrome (MeSH)

ORGN . . .

Taxa Notes

Animals, Artiodactyls, Chordates, Mammals, Nonhuman Vertebrates,
Nonhuman Mammals, Vertebrates

ORGN Classifier

Viruses 03000

Super Taxa

Microorganisms

Organism Name

prion : pathogen

Taxa Notes

Microorganisms, Viruses

L12 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 1999:489859 BIOSIS

DN PREV199900489859

TI Immunological characterization of the sheep ***prion*** protein
expressed as fusion proteins in Escherichia coli.

AU Baron, Thierry G. M. [Reprint author]; Betemps, Dominique; Groschup,
Martin H.; Madec, Jean-Yves

CS Agence Francaise de Securite Sanitaire des Aliments, 31, avenue Tony
Garnier, 69342, Lyon Cedex 07, France

SO FEMS Immunology and Medical Microbiology, (Sept., 1999) Vol. 25, No. 4,
pp. 379-384. print.
ISSN: 0928-8244.

DT Article

LA English

ED Entered STN: 16 Nov 1999

Last Updated on STN: 16 Nov 1999

AB The ***prion*** protein (PrP) from sheep was produced in large quantities of entire protein in Escherichia coli after fusion with a carboxy-terminal hexahistidine sequence. In contrast, amino-terminal fusion with glutathione S-transferase (GST) revealed a high susceptibility toward cleavage of the protein. Both recombinant proteins were recognised, at variable levels, in Western blots using a panel of antibodies against the 40-56, 89-104, 98-113 and 112-115 sequences of the ***prion*** protein, similarly to the ***abnormal*** ***prion*** protein extracted from scrapie-infected sheep. Interestingly, ***monoclonal*** antibody 3F4 was found to react with these three proteins in Western blot.

TI Immunological characterization of the sheep ***prion*** protein expressed as fusion proteins in Escherichia coli.

AB The ***prion*** protein (PrP) from sheep was produced in large quantities of entire protein in Escherichia coli after fusion with a carboxy-terminal. . . variable levels, in Western blots using a panel of antibodies against the 40-56, 89-104, 98-113 and 112-115 sequences of the ***prion*** protein, similarly to the ***abnormal*** ***prion*** protein extracted from scrapie-infected sheep. Interestingly, ***monoclonal*** antibody 3F4 was found to react with these three proteins in Western blot.

IT . . .
System (Chemical Coordination and Homeostasis); Infection; Veterinary Medicine (Medical Sciences)

IT Diseases
scrapie infection: disease-miscellaneous
Scrapie (MeSH)

IT Chemicals & Biochemicals
monoclonal antibody 3F4; scrapie agent; sheep ***prion*** protein [sPrP]: cleavage, immunological characterization; GST [glutathione-S-transferase]

L12 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:629676 CAPLUS

TI Simple and specific detection of ***abnormal*** ***prion*** protein by laser-induced fluorescence immunoassay

AU Kim, Jae-II; Kuizon, Salomon; Wang, Chuanhua; Papini, Michael; Karpinska, Ewa; Gray, Perry C.; Rubenstein, Richard

CS New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, 10314, USA

SO Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), ANYL-014 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69EKY9

DT Conference; Meeting Abstract

LA English

AB Laser-induced fluorescence (LIF) is useful for obtaining measurements on fluorescence-labeled targets with a high degree of sensitivity. In the present study, we applied this technol. to the immunol. detection of ***abnormal*** ***prion*** protein, PrPSc, which is a universal diagnostic marker for transmissible spongiform encephalopathies (TSEs). The assay format consists of a magnetic bead-based sandwich immunoassay utilizing a biotin-conjugated capture antibody and a fluorophore-labeled detector antibody. By using pair of anti-PrP ***monoclonal*** antibodies, PrPSc in brain homogenates from various exptl. and natural TSEs can be easily detected with high specificity. Furthermore, the assay proved to be applicable for the detection of PrPSc in the lymph nodes from deer and elk with TSEs (with a specificity of 100%). While sensitivity of the assay was shown to be comparable to std. immunoblotting, this system has several advantages over conventional tests, in terms of simplicity, specificity, and run time. These results provide valuable data for the

development of an early diagnostic test and will lead to an important basis for multi-sample anal.

TI Simple and specific detection of ***abnormal*** ***prion*** protein by laser-induced fluorescence immunoassay

AB Laser-induced fluorescence (LIF) is useful for obtaining measurements on fluorescence-labeled targets with a high degree of sensitivity. In the present study, we applied this technol. to the immunol. detection of ***abnormal*** ***prion*** protein, PrPSc, which is a universal diagnostic marker for transmissible spongiform encephalopathies (TSEs). The assay format consists of a magnetic bead-based sandwich immunoassay utilizing a biotin-conjugated capture antibody and a fluorophore-labeled detector antibody. By using pair of anti-PrP ***monoclonal*** antibodies, PrPSc in brain homogenates from various exptl. and natural TSEs can be easily detected with high specificity. Furthermore, the assay proved to be applicable for the detection of PrPSc in the lymph nodes from deer and elk with TSEs (with a specificity of 100%). While sensitivity of the assay was shown to be comparable to std. immunoblotting, this system has several advantages over conventional tests, in terms of simplicity, specificity, and run time. These results provide valuable data for the development of an early diagnostic test and will lead to an important basis for multi-sample anal.

L12 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2003:349832 CAPLUS

DN 138:365135

TI Immunoassay reagent and kit for measuring abnormal-type ***prion*** , and immunoassay method for measuring abnormal-type ***prion*** using reagent or kit

IN Shinagawa, Shinichi; Horiuchi, Motohiro; Yanagitani, Takayuki; Matsui, Toshio; Umetani, Atsushi

PA Fujirebio, Inc., Japan

SO Jpn. Kokai Tokkyo Koho, 9 pp.

CODEN: JKXXAF

DT Patent

LA Japanese

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI JP 2003130880	A2	20030508	JP 2001-330696	20011029
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PRAI JP 2001-330696		20011029		
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AB An immunoassay method is provided for detecting the abnormal-type ***prion*** with high sensitivity without performing a time-consuming electrophoresis operation or centrifugation operation. Also provided is an immunoassay reagent for this method, which is prepd. by immobilizing a first antibody immunol. reactive with the abnormal-type ***prion*** treated with a denaturing agent (e.g., guanidine, guanidine thiocyanate) on magnetic particles. The method comprises a process for treating a sample potentially contg. the abnormal-type ***prion*** with a surfactant, collagenase and a proteinase (e.g., proteinase K), a process for treating the product obtained with a denaturing agent without having a centrifuge operation, and a process for immunol. assaying the product with the immunoassay reagent.

TI Immunoassay reagent and kit for measuring abnormal-type ***prion*** , and immunoassay method for measuring abnormal-type ***prion*** using reagent or kit

AB An immunoassay method is provided for detecting the abnormal-type ***prion*** with high sensitivity without performing a time-consuming electrophoresis operation or centrifugation operation. Also provided is an immunoassay reagent for this method, which is prepd. by immobilizing a first antibody immunol. reactive with the abnormal-type ***prion*** treated with a denaturing agent (e.g., guanidine, guanidine thiocyanate)

on magnetic particles. The method comprises a process for treating a sample potentially contg. the abnormal-type ***prion*** with a surfactant, collagenase and a proteinase (e.g., proteinase K), a process for treating the product obtained with a denaturing agent without having a centrifuge operation, and a process for immunol. assaying the product with the immunoassay reagent.

ST ***abnormal*** ***prion*** protein immunoassay

IT Proteins

RL: ARU (Analytical role, unclassified); CPS (Chemical process); PEP (Physical, engineering or chemical process); ANST (Analytical study); PROC (Process)

(G; immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT ***Prion*** proteins

RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)

(PrPc, mouse; recombinant; immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT ***Prion*** proteins

RL: ANT (Analyte); BPN (Biosynthetic preparation); BUU (Biological use, unclassified); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(PrPSc, mouse; immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT Immobilization, molecular

Immunoassay

Magnetic particles

Prion diseases

Surfactants

Test kits

(immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT Antibodies

RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); CPS (Chemical process); PEP (Physical, engineering or chemical process); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT Antibodies

RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(***monoclonal*** , 44B1 (FERM P-18515), 72-5 (FERM P-18516); immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT Antibodies

RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses) (secondary; immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT 50-01-1, Guanidine hydrochloride 113-00-8, Guanidine 593-84-0, Thiocyanic acid, compd. with guanidine (1:1) 9001-12-1, Collagenase 39450-01-6, Proteinase, Tritirachium album serine

RL: ARU (Analytical role, unclassified); ANST (Analytical study)

(immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT 9001-92-7, Proteinase

RL: ARU (Analytical role, unclassified); ANST (Analytical study)

(protease, and inhibitor; immunoassay for measuring abnormal-type ***prion*** using reagent or kit)

IT 521340-46-5 521340-47-6

RL: PRP (Properties)
(unclaimed nucleotide sequence; immunoassay reagent and kit for measuring abnormal-type ***prion***, and immunoassay method for measuring abnormal-type ***prion*** using reagent or kit)

L12 ANSWER 8 OF 23 JAPIO (C) 2003 JPO on STN

AN 2003-144148 JAPIO

TI ***MONOCLONAL*** ANTIBODY TO ***PRION*** PROTEIN
IN TSUKUI KAZUO

PA NIPPON SEKIJIYUJISHIYA

ONODERA SETSU

PI JP 2003144148 A 20030520 Heisei

AI JP 2001-352119 (JP2001352119 Heisei) 20011116

PRAI JP 2001-352119 20011116

SO PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2003

AB PROBLEM TO BE SOLVED: To provide a ***monoclonal*** antibody reactive to either of normal ***prion*** and ***abnormal*** ***prion*** derived from different animal species.

SOLUTION: This ***monoclonal*** antibody is obtained by the following process: for example, ***prion*** protein knockout mouse (PrP<SP>0/0</SP>) is immunized with ***prion*** protein, the splenocyte from the thus immunized animal is hybridized with e.g. lymphoblast, and hybridoma cells which acquired HAT resistance in a HAT selective medium are obtained, and from the resulting cell group, the clone in production of the objective antibody meeting the above-mentioned reactivity. For the analysis of the antibody's characteristics, its recognition reactivity to recombinant ***prion*** protein and natural ***prion*** protein derived from a plurality of animal species is assessed by the use of a combination of immunoprecipitation method with Western blotting method.

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TI ***MONOCLONAL*** ANTIBODY TO ***PRION*** PROTEIN

AB PROBLEM TO BE SOLVED: To provide a ***monoclonal*** antibody reactive to either of normal ***prion*** and ***abnormal*** ***prion*** derived from different animal species.

SOLUTION: This ***monoclonal*** antibody is obtained by the following process: for example, ***prion*** protein knockout mouse (PrP<SP>0/0</SP>) is immunized with ***prion*** protein, the splenocyte from the thus immunized animal is hybridized with e.g. lymphoblast, and hybridoma cells which acquired HAT resistance. . . of the objective antibody meeting the above-mentioned reactivity. For the analysis of the antibody's characteristics, its recognition reactivity to recombinant ***prion*** protein and natural ***prion*** protein derived from a plurality of animal species is assessed by the use of a combination of immunoprecipitation method with. . .

L12 ANSWER 9 OF 23 LIFESCI COPYRIGHT 2003 CSA on STN

AN 91:53058 LIFESCI

TI Abnormal isoform of ***prion*** protein accumulates in follicular dendritic cells in mice with Creutzfeldt-Jakob disease.

AU Kitamoto, T.; Muramoto, T.; Mohri, S.; Doh-Ura, K.; Tateishi, J.

CS Dep. Neuropathol., Fac. Med., Kyushu Univ., Fukuoka 812, Japan

SO J. VIROL., (1991) vol. 65, no. 11, pp. 6292-6295.

DT Journal

FS V

LA English

SL English

AB We established that follicular dendritic cells (FDCs) are the site of ***abnormal*** ***prion*** protein (PrP super(CJD)) accumulations in lymphoid tissues from mice infected with Creutzfeldt-Jakob disease. Evidence of positive FDC staining was observed in Creutzfeldt-Jakob

disease-infected mice irrespective of the inoculation route, while no such staining was seen in the control mice. We also found that the severe combined immunodeficiency mouse trait is transmittable via the intracranial route but not via the intraperitoneal route. Mice with severe combined immunodeficiency did not have PrP super(CJD) accumulation in FDCs.

TI Abnormal isoform of ***prion*** protein accumulates in follicular dendritic cells in mice with Creutzfeldt-Jakob disease.

AB We established that follicular dendritic cells (FDCs) are the site of ***abnormal*** ***prion*** protein (PrP super(CJD)) accumulations in lymphoid tissues from mice infected with Creutzfeldt-Jakob disease. Evidence of positive FDC staining was observed. . .

UT ***prions*** ; accumulation; dendrites; immunohistochemistry; ***monoclonal*** antibodies; mice; Creutzfeldt-Jakob disease

L12 ANSWER 10 OF 23 MEDLINE on STN

AN 2001678857 MEDLINE

DN 21581981 PubMed ID: 11724899

TI Immunohistochemistry of PrPsc within bovine spongiform encephalopathy brain samples with graded autolysis.

AU Debeer S O; Baron T G; Bencsik A A

CS AFSSA, Laboratoire d'Etudes et de Recherches en Pathologie Bovine et Hygiene des Viandes, Unite Virologie-ATNC, Lyon, France..
s.debeer@lyon.afssa.fr

SO JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (2001 Dec) 49 (12) 1519-24.
Journal code: 9815334. ISSN: 0022-1554.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200201

ED Entered STN: 20011129

Last Updated on STN: 20020125

Entered Medline: 20020117

AB Bovine spongiform encephalopathy (BSE) is a transmissible neurodegenerative disease of cattle. Clinical diagnosis can be confirmed by investigation of both spongiform changes and ***abnormal*** ***prion*** protein (PrPsc), a marker considered specific for the disease. Tissue autolysis, often unavoidable in routine field cases, is not compatible with histological examination of the brain even though PrPsc is still detectable by immunoblotting. To determine how autolysis might affect accurate diagnosis using PrPsc immunohistochemistry, we studied 50 field samples of BSE brainstem (obex) with various degrees of autolysis. We demonstrated that the antigen-unmasking pretreatments necessary for PrPsc immunohistochemistry were compatible with the preservation of autolyzed brain sections and that PrPsc detection was unaffected by autolysis, even though anatomic markers were sometimes lost. In tissue samples in which anatomic sites were still recognizable, PrPsc accumulation was detected in specific gray matter nuclei. In samples with advanced autolysis, PrPsc deposits were still observed, at least at the cellular level, as an intraneuronal pattern. We found that the sensitivity of PrPsc immunohistochemistry as a diagnostic method for BSE was undiminished even by severe tissue autolysis.

AB . . . (BSE) is a transmissible neurodegenerative disease of cattle. Clinical diagnosis can be confirmed by investigation of both spongiform changes and ***abnormal*** ***prion*** protein (PrPsc), a marker considered specific for the disease. Tissue autolysis, often unavoidable in routine field cases, is not compatible. . .

CT Check Tags: Animal; Support, Non-U.S. Gov't

*** Antibodies, Monoclonal***

*Autolysis

Biological Markers: AN, analysis
*Brain: ME, metabolism
Brain: PA, pathology
Brain Stem: ME, metabolism
Brain Stem: PA, . . .
CN 0 (Antibodies, ***Monoclonal***); 0 (Biological Markers); 0 (PrPSc
Proteins)

L12 ANSWER 11 OF 23 MEDLINE on STN

AN 2000481675 MEDLINE

DN 20400795 PubMed ID: 10940676

TI Differential expression of metallothioneins in human ***prion***
diseases.

AU Kawashima T; Doh-ura K; Torisu M; Uchida Y; Furuta A; Iwaki T

CS Department of Neuropathology, Neurological Institute, Graduate School of
Medical Sciences, Kyushu University, Fukuoka, Japan..
toshiro@npsych.med.kyushu-u.ac.jp

SO DEMENTIA AND GERIATRIC COGNITIVE DISORDERS, (2000 Sep-Oct) 11 (5) 251-62.
Journal code: 9705200. ISSN: 1420-8008.

CY Switzerland

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200010

ED Entered STN: 20001019

Last Updated on STN: 20001019

Entered Medline: 20001011

AB We herein report an immunohistochemical and a Western blot analysis on
metal/free radical chelating proteins, metallothioneins (MTs; MT-I/II and
MT-III), in the brains of human ***prion*** disease patients with or
without ***prion*** protein gene mutation and polymorphism.
Irrespective of the isoforms of MTs, the immunoreaction was detected in
the cytoplasm and processes of the astrocytes in the cerebral cortex and
white matter in normal controls and ***prion*** disease brains.
Although the immunoreactivities for MTs in Creutzfeldt-Jakob disease (CJD)
brains varied from case to case, they were generally dependent upon the
disease duration. In CJD patients with a relatively long disease course,
the immunoreaction for both MT-I/II and MT-III in the astrocytes was
significantly reduced, and this finding was not modified by the genotypes
of the patients. On the other hand, in patients with Gerstmann-Straussler-
Scheinker syndrome, MT-I/II immunoreactivity in the astrocytes was
exclusively reduced, while the immunoreaction for MT-III was relatively
well preserved. Especially the astrocytes in the vicinities of the kuru
plaques exhibited a weak or no immunoreaction even for MTs but a strong
immunoreaction for glial fibrillary acidic protein. A quantitative
Western blot analysis also revealed that MT-I/II protein accumulated in
CJD brain with a short disease duration, whereas MT-III in CJD brain with
a long disease duration was statistically significantly reduced in
comparison to the normal brains. These findings suggest that the protein
expression of MTs in the astrocytes is thus regulated differentially among
human ***prion*** diseases and modified locally by such
abnormal ***prion*** protein depositions as kuru plaques.

Copyright 2000 S. Karger AG, Basel

TI Differential expression of metallothioneins in human ***prion***
diseases.

AB . . . and a Western blot analysis on metal/free radical chelating
proteins, metallothioneins (MTs; MT-I/II and MT-III), in the brains of
human ***prion*** disease patients with or without ***prion***
protein gene mutation and polymorphism. Irrespective of the isoforms of
MTs, the immunoreaction was detected in the cytoplasm and processes of the
astrocytes in the cerebral cortex and white matter in normal controls and

prion disease brains. Although the immunoreactivities for MTs in Creutzfeldt-Jakob disease (CJD) brains varied from case to case, they were generally. . . normal brains. These findings suggest that the protein expression of MTs in the astrocytes is thus regulated differentially among human ***prion*** diseases and modified locally by such ***abnormal*** ***prion*** protein depositions as kuru plaques.

Copyright 2000 S. Karger AG, Basel

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't

Adult

Aged

Aged, 80 and over

*** Antibodies, Monoclonal: IM, immunology***

*** Antibodies, Monoclonal: ME, metabolism***

Blotting, Western

Brain Chemistry: PH, physiology

Creutzfeldt-Jakob Syndrome: ME, metabolism

Ferritin: BI, biosynthesis

Ferritin: GE, genetics

. . . Glial Fibrillary Acidic Protein: BI, biosynthesis

Glial Fibrillary Acidic Protein: GE, genetics

Immunohistochemistry

*Metallothionein: BI, biosynthesis

Middle Age

Molecular Weight

****Prion Diseases: ME, metabolism***

*** Prions: BI, biosynthesis***

*** Prions: GE, genetics***

CN 0 (Antibodies, ***Monoclonal***); 0 (Glial Fibrillary Acidic Protein);

0 (***Prions***)

L12 ANSWER 12 OF 23 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AN 2003:803966 SCISEARCH

GA The Genuine Article (R) Number: 720DT

TI Molecular analysis of cases of Italian sheep scrapie and comparison with cases of bovine spongiform encephalopathy (BSE) and experimental BSE in sheep

AU Nonno R (Reprint); Esposito E; Vaccari G; Conte M; Marcon S; Di Bari M; Ligios C; Di Guardo G; Agrimi U

CS Ist Super Sanita, Lab Vet Med, Viale Regina Elena 299, I-00161 Rome, Italy (Reprint); Ist Super Sanita, Lab Vet Med, I-00161 Rome, Italy; Ist Zooprofilattico Sperimentale Lazio & Toscana, Rome, Italy; Ist Zooprofilattico Sperimentale Sardegna, Sassari, Italy

CYA Italy

SO JOURNAL OF CLINICAL MICROBIOLOGY, (SEP 2003) Vol. 41, No. 9, pp. 4127-4133.

Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA.

ISSN: 0095-1137.

DT Article; Journal

LA English

REC Reference Count: 39

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Concerns have been raised about the possibility that the bovine spongiform encephalopathy (BSE) agent could have been transmitted to sheep populations via contaminated feedstuffs. The objective of our study was to investigate the suitability of molecular strain typing methods as a surveillance tool for studying scrapie strain variations and for differentiating PrPSc from sheep scrapie, BSE, and sheep BSE. We studied 38 Italian sheep scrapie cases from 13 outbreaks, along with a British scrapie case, an experimental ovine BSE, and 3 BSE cases, by analyzing the glycoform patterns and the apparent molecular masses of the

nonglycosylated forms of semipurified, proteinase-treated PrPSc. Both criteria were able to clearly differentiate sheep scrapie from BSE and ovine experimental BSE. PrPSc from BSE and sheep BSE showed a higher glycoform ratio and a lower molecular mass of the nonglycosylated form compared to scrapie PrPSc. Scrapie cases displayed homogeneous PrPSc features regardless of breed, Hock, and geographic origin. The glycoform patterns observed varied with the antibody used, but either a ***monoclonal*** antibody (MAb) (F99/97.6.1) or a polyclonal antibody (P7-7) was able to distinguish scrapie from BSE PrPSc. While more extensive surveys are needed to further corroborate these findings, our results suggest that large-scale molecular screening of sheep populations for BSE surveillance may be eventually possible.

AB . . . features regardless of breed, Hock, and geographic origin. The glycoform patterns observed varied with the antibody used, but either a ***monoclonal*** antibody (MAb) (F99/97.6.1) or a polyclonal antibody (P7-7) was able to distinguish scrapie from BSE PrPSc. While more extensive surveys. . .

STP KeyWords Plus (R): ***ABNORMAL*** ***PRION*** PROTEIN; STRAIN VARIATION; NATURAL SCRAPIE; INFECTED SHEEP; VARIANT CJD; BREED SHEEP; AGENT; PRP; TRANSMISSION; MICE

L12 ANSWER 13 OF 23 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AN 2002:815664 SCISEARCH

GA The Genuine Article (R) Number: 597BX

TI PrPCWD lymphoid cell targets in early and advanced chronic wasting disease of mule deer

AU Sigurdson C J; Barillas-Mury C; Miller M W; Oesch B; van Keulen L J M; Langeveld J P M; Hoover E A (Reprint)

CS Colorado State Univ, Coll Vet Med & Biomed Sci, Dept Microbiol Immunol & Pathol, Ft Collins, CO 80523 USA (Reprint); Colorado Div Wildlife, Wildlife Res Ctr, Ft Collins, CO 80526 USA; Prion AG, CH-8952 Schlieren, Switzerland; Inst Anim Sci & Hlth, ID Lelystad, NL-8219 PH Lelystad, Netherlands

CYA USA; Switzerland; Netherlands

SO JOURNAL OF GENERAL VIROLOGY, (OCT 2002) Vol. 83, Part 10, pp. 2617-2628.

Publisher: SOC GENERAL MICROBIOLOGY, MARLBOROUGH HOUSE, BASINGSTOKE RD, SPENCERS WOODS, READING RG7 1AE, BERKS, ENGLAND.

ISSN: 0022-1317.

DT Article; Journal

LA English

REC Reference Count: 60

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Up to 15% of free-ranging mule deer in northeastern Colorado and southeastern Wyoming, USA, are afflicted with a ***prion*** disease, or transmissible spongiform encephalopathy (TSE), known as chronic wasting disease (CWD). CWD is similar to a subset of TSEs including scrapie and variant Creutzfeldt-Jakob disease in which the ***abnormal*** ***prion*** protein isoform, PrPCWD, accumulates in lymphoid tissue. Experimental scrapie studies have indicated that this early lymphoid phase is an important constituent of ***prion*** replication interposed between mucosal entry and central nervous system accumulation. To identify the lymphoid target cells associated with PrPCWD, we used triple-label immunofluorescence and high-resolution confocal microscopy on tonsils from naturally infected deer in advanced disease. We detected PrPCWD primarily extracellularly in association with follicular dendritic and IS cell membranes as determined by frequent co-localization with antibodies against membrane bound immunoglobulin and CD21. There was minimal co-localization with cytoplasmic labels for follicular dendritic cells (FDC). This finding could indicate FDC capture of PrPCWD, potentially in association with immunoglobulin or complement, or PrPC conversion on FDC. In addition, scattered tingible body macrophages in the germinal centre

contained coarse intracytoplasmic aggregates of PrPCWD, reflecting either phagocytosis of PrPCWD on FDC processes, apoptotic FDC or B cells, or actual PrPCWD replication within tingible body macrophages. To compare lymphoid cell targets in early and advanced disease, we also examined: (i) PrPCWD distribution in lymphoid cells of fawns within 3 months of oral CWD exposure and (ii) tonsil biopsies from preclinical deer with naturally acquired CWD. These studies revealed that the early lymphoid cellular distribution of PrPCWD was similar to that in advanced disease, i.e. in a pattern suggesting FDC association. We conclude that in deer, PrPCWD accumulates primarily extracellularly and associated with FDCs and possibly B cells - a finding which raises questions as to the cells responsible for pathological ***prion*** production.

AB Up to 15% of free-ranging mule deer in northeastern Colorado and southeastern Wyoming, USA, are afflicted with a ***prion*** disease, or transmissible spongiform encephalopathy (TSE), known as chronic wasting disease (CWD). CWD is similar to a subset of TSEs including scrapie and variant Creutzfeldt-Jakob disease in which the ***abnormal*** ***prion*** protein isoform, PrPCWD, accumulates in lymphoid tissue. Experimental scrapie studies have indicated that this early lymphoid phase is an important constituent of ***prion*** replication interposed between mucosal entry and central nervous system accumulation. To identify the lymphoid target cells associated with PrPCWD, we . . . associated with FDCs and possibly B cells - a finding which raises questions as to the cells responsible for pathological ***prion*** production.

STP KeyWords Plus (R): FOLLICULAR DENDRITIC CELLS; CREUTZFELDT-JAKOB-DISEASE; IMMUNODEFICIENCY-VIRUS TYPE-1; SPONGIFORM ENCEPHALOPATHY BSE; CERVUS-ELAPHUS-NELSONI; ***PRION*** PROTEIN; ***MONOCLONAL*** -ANTIBODY; ODOCOILEUS-HEMIONUS; NATURAL SCRAPIE; IMMUNOHISTOCHEMICAL DETECTION

L12 ANSWER 14 OF 23 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AN 2000:717663 SCISEARCH

GA The Genuine Article (R) Number: 354ZV

TI Enhanced CD9 expression in the mouse and human brains infected with transmissible spongiform encephalopathies

AU Dohura K (Reprint); Mekada E; Ogomori K; Iwaki T

CS KYUSHU UNIV, GRAD SCH MED SCI, NEUROL INST, DEPT NEUROPATHOL, HIGASHI KU, 3-1-1 MAIDASHI, FUKUOKA 8128582, JAPAN (Reprint); KYUSHU UNIV, DEPT PSYCHIAT, HIGASHI KU, FUKUOKA 8128582, JAPAN; OSAKA UNIV, MICROBIAL DIS RES INST, DEPT MOL EMBRYOL, OSAKA, JAPAN

CYA JAPAN

SO JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (SEP 2000) Vol. 59, No. 9, pp. 774-785.

Publisher: AMER ASSN NEUROPATHOLOGISTS INC, 1041 NEW HAMPSHIRE ST, LAWRENCE, KS 66044.

ISSN: 0022-3069.

DT Article; Journal

FS LIFE

LA English

REC Reference Count: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A tetraspan protein CD9, normally expressed in the myelin sheath of the central and peripheral nervous system, was identified to be up-regulated in mouse brains infected with transmissible spongiform encephalopathy (TSE), by mRNA differential display screening. To elucidate its role in the neurodegeneration process observed in TSE, CD9 expression was examined in the murine disease model and in the human disease materials. Up-regulation of CD9 gene expression in the TSE-infected mouse brains was detected as early as a preclinical stage, when ***abnormal*** ***prion*** protein deposition and vacuolation were obviously manifested in the internal capsule and thalamus. In contrast, other myelin protein

genes showed a reverse pattern of CD9 gene expression. Enhanced CD9 expression was immunohistochemically detected in the astrocytes of such pathological regions. In human specimens of TSE, enhanced CD9 immunoreactivity was observed in the astrocytes and some oligodendrocytes in the brains, but no relevant alteration in CD9 immunoreactivity was observed in the other organs or tissues. Positive CD9 immunoreactivity in astrocytes was also manifest in other neurological disorders in a less prominent manner. The findings indicate that up-regulated CD9 plays a role in glial cells in pathological conditions, especially in such a devastating condition as TSE.

AB . . . materials. Up-regulation of CD9 gene expression in the TSE-infected mouse brains was detected as early as a preclinical stage, when ***abnormal*** ***prion*** protein deposition and vacuolation were obviously manifested in the internal capsule and thalamus. In contrast, other myelin protein genes showed. . .

STP KeyWords Plus (R): PERIPHERAL NERVOUS SYSTEMS; CREUTZFELDT-JAKOB-DISEASE; MIGRATION IN-VITRO; GENE-EXPRESSION; ***PRION*** PROTEIN; ***MONOCLONAL*** -ANTIBODY; MEMBRANE-PROTEIN; MESSENGER-RNA; SCRAPIE; ACTIVATION

L12 ANSWER 15 OF 23 USPATFULL on STN

AN 2003:251654 USPATFULL

TI Pyridylpyrimidine derivatives as effective compounds against ***prion*** diseases

IN Stein-Gerlach, Matthias, Munich, GERMANY, FEDERAL REPUBLIC OF
Salassidis, Konstadinos, Ehcing, GERMANY, FEDERAL REPUBLIC OF
Bacher, Gerald, Germering, GERMANY, FEDERAL REPUBLIC OF
Muller, Stefan, Munich, GERMANY, FEDERAL REPUBLIC OF

PI US 2003176443 A1 20030918

AI US 2002-204041 A1 20020816 (10)

WO 2002-EP5420 20020516

PRAI EP 2001-111858 20010516

EP 2001-117113 20010713

DT Utility

FS APPLICATION

LREP Leon R Yankwich, Yankwich & Associates, 201 Broadway, Cambridge, MA,
02139

CLMN Number of Claims: 48

ECL Exemplary Claim: 1

DRWN 3 Drawing Page(s)

LN.CNT 3218

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to pyridylpyrimidine derivatives of the general formula (I): ##STR1##

wherein R represents hydrogen or methyl and Z represents nitrogen containing functional groups, the use of the pyridylpyrimidine derivatives as pharmaceutically active agents, especially for the prophylaxis and/or treatment of ***prion*** infections and ***prion*** diseases, as well as compositions containing at least one pyridylpyrimidine derivative and/or pharmaceutically acceptable salt thereof. Furthermore, the present invention is directed to methods for preventing and/or treating ***prion*** infections and ***prion*** diseases using said pyridylpyrimidine derivatives. Human cellular protein kinases, phosphatases and cellular signal transduction molecules are disclosed as targets for detecting, preventing and/or treating ***prion*** infections and diseases, especially BSE, vCJD, or CJD which can be inhibited by the inventive pyridylpyrimidine derivatives.

TI Pyridylpyrimidine derivatives as effective compounds against ***prion*** diseases

AB . . . containing functional groups, the use of the pyridylpyrimidine

derivatives as pharmaceutically active agents, especially for the prophylaxis and/or treatment of ***prion*** infections and ***prion*** diseases, as well as compositions containing at least one pyridylpyrimidine derivative and/or pharmaceutically acceptable salt thereof. Furthermore, the present invention is directed to methods for preventing and/or treating ***prion*** infections and ***prion*** diseases using said pyridylpyrimidine derivatives. Human cellular protein kinases, phosphatases and cellular signal transduction molecules are disclosed as targets for detecting, preventing and/or treating ***prion*** infections and diseases, especially BSE, vCJD, or CJD which can be inhibited by the inventive pyridylpyrimidine derivatives.

SUMM . . . to pyridylpyrimidine derivatives, the use of the pyridylpyrimidine derivatives as pharmaceutically active agents, especially for the prophylaxis and/or treatment of ***prion*** infections and ***prion*** diseases, as well as compositions containing at least one pyridylpyrimidine derivative and/or pharmaceutically acceptable salt thereof, and methods for preventing and/or treating ***prion*** infections and ***prion*** diseases. Furthermore, human cellular protein kinases, phosphatases and cellular signal transduction molecules are disclosed as targets for detecting, preventing and/or treating ***prion*** infections and diseases, especially BSE, vCJD, or CJD.

SUMM [0003] ***Prions*** are infectious agents which do not have a nucleic acid genome. It seems that a protein alone is the infectious agent. A ***prion*** has been defined as "small proteinaceous infectious particle which resists inactivation by procedures that modify nucleic acids". The discovery that proteins alone can transmit an infectious disease has come as a considerable surprise to the scientific community. ***Prion*** diseases are often called "transmissible spongiform encephalopathies", because of the post mortem appearance of the brain with large vacuoles in the cortex and cerebellum. Probably most mammalian species develop these diseases. ***Prion*** diseases are a group of neurodegenerative disorders of humans and animals and the ***prion*** diseases can manifest as sporadic, genetic or infectious disorders. Examples for ***prion*** diseases acquired by exogenous infection are the Bovine spongiform encephalitis (BSE) of cattle and the new variant of Creutzfeld-Jakob disease. . . by BSE. Further examples include kuru, Gerstmann-Straussler-Scheinker disease of humans as well as scrapie of animals. For many years, the ***prion*** diseases were thought to be caused by viruses despite intriguing evidence to the contrary. The unique characteristic common to all. . . of these disorders, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of the ***prion*** protein (PrP). In many cases, the cellular ***prion*** protein (PrP^{sup.c}) ["c" refers to cellular] is converted into the scrapie isoform (PrP^{sup.Sc}) ["Sc" refers to Scrapie] by a posttranslational process that involves a conformational change. Often, the human ***prion*** diseases are transmissible to experimental animals and all of the inherited ***prion*** diseases segregate with PrP gene mutations.

SUMM [0004] These ***prion*** diseases in animals and humans have a long incubation period and a long clinical course, and are always fatal leading. . .

SUMM [0008] The medical need in ***prion*** diseases today can be clearly defined as the establishment of a diagnostic system, that can detect the disease as early. . . in the future and to identify the infected animals to remove them from the food chain. The medical need for ***prion*** diseases in the future (approximately starting in 5-10 years) will be medical treatment that inhibits the disease symptoms, the manifestation. . .

SUMM . . . provide novel and also known compounds which can be used as

pharmaceutically active agents, especially for prophylaxis and/or treatment of ***prion*** infections and ***prion*** diseases, methods wherein said compounds are used in order to treat ***prion*** infections and ***prion*** diseases and compositions containing at least one inventive compound and/or pharmaceutically acceptable salt thereof as a pharmaceutically active ingredient.

SUMM . . . herein, the present invention discloses the use of compounds of the general formula (I) for the prophylaxis and/or treatment of ***prion*** infections and ***prion*** diseases. As described above, said pyridylpyrimidine derivatives have first of all been used in tumor therapy. The Novartis compound Gleevec.TM.. . . in many countries as anticancer drug. This Gleevec.TM. compound (compound 53) is also the most active one in the indication ***prion*** diseases.

SUMM [0027] The name " ***prion*** " is used to describe the causative agents which underlie the transmissible spongiform encephalopathies. A ***prion*** is proposed to be a novel infectious particle that differs from viruses and viroids. It is composed solely of one. . . inactivation procedures such as heat, radiation, and proteases. The latter characteristic has led to the term protease-resistant isoform of the ***prion*** protein. The protease-resistant isoform has been proposed to slowly catalyze the conversion of the normal ***prion*** protein into the abnormal form.

SUMM [0028] The term "isoform" in the context of ***prions*** means two proteins with exactly the same amino acid sequence that are folded into molecules with dramatically different tertiary structures. The normal cellular isoform of the ***prion*** protein (PrP.sup.c) has a high .alpha.-helix content, a low .beta.-sheet content, and is sensitive to protease digestion. The abnormal, disease-causing. . .

SUMM . . . signal transduction molecules may lead to the malfunctioning of cells and disease processes. Specifically, interference of the pathogenic PrP.sup.Sc from ***prion*** diseases with neuronal cells is necessary for the ***prion*** protein to induce its neuropathological features such as neuronal vacuolization, neuronal death and gliosis with hyperastrocytosis.

SUMM . . . serve as targets and are inhibited by the pyridylpyrimidine compounds of the general formula (I). It could be proved that ***prion*** infections and/or ***prion*** diseases can be treated and also be prevented by the inhibition of said kinase Abl using the inventive pyridylpyrimidine derivatives.. . .

SUMM . . . the filters, the expression pattern of signal transduction mRNAs in neuronal mouse cells transfected with the pathogenic form of the ***prion*** protein (PrP.sup.Sc) were compared with the same cells transfected with the non-pathogenic wild-type form (PrP.sup.c) as a control. Interference of. . .

SUMM . . . protein phosphatases PTP-SL (also known as MCP83), PTP-zeta, the cellular signal transduction molecules HSP86, and GPIR-1 were identified as potential anti- ***prion*** disease targets. Said cellular protein kinases, phosphatases and signal transduction molecules are found to be specifically up- or downregulated by. . .

SUMM [0130] Surprisingly, it was found that the following human cellular targets are significantly up- or downregulated in ***prion*** infected cells:

target	regulation
FGF-R1	3.6 fold stronger
Abl	5.6 fold stronger
MKK7	4.1 fold stronger
CDC2	2.0. . .

SUMM [0131] Thus, one aspect of the present invention relates to a method for

preventing and/or treating ***prion*** infections and/or diseases associated with said ***prion*** infections in an individual which comprises administering to the individual an amount of at least one compound of the general formula (I) and/or pharmaceutically acceptable salts thereof effective to prevent and/or treat said ***prion*** infections and/or ***prion*** diseases. Most preferred is the administration of a compound according to claim 8.

SUMM . . . from FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 was effective to treat ***prion*** diseases. Therefore, another aspect of the invention relates to a method for preventing and/or treating ***prion*** infections and/or ***prion*** diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one compound according of. . .

SUMM . . . PTP-SL, PTP-zeta, HSP86, GPIR-1 by the use of a method for detecting compounds useful for the prophylaxis and/or treatment of ***prion*** infections and/or diseases. Said method comprises

SUMM . . . the up- or downregulation of the above-mentioned human cellular protein kinases, phosphatases, or cellular signal transduction molecules specifically involved in ***prion*** infections and/or diseases.

Thus, the present invention is also directed to a method for detecting ***prion*** infections and/or diseases in an individual comprising:

SUMM [0146] A similar aspect of the present invention is directed to a method for detecting ***prion*** infections and/or ***prion*** diseases in cells, cell cultures and/or cell lysates comprising:

SUMM . . . Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, GPIR-1 has an effect on the production of ***prions***. Therefore, another aspect of the invention relates to a method for regulating the production of ***prions*** in an individual or in cells comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically. .

SUMM [0152] Another type of pharmaceutically active agents useful within the methods disclosed herein are ***monoclonal*** or polyclonal antibodies which bind to a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from. . . JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1. Thus, a further aspect of the present invention is related to said ***monoclonal*** or polyclonal antibodies which bind to a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from. .

SUMM . . . invention utilizes the scientific findings that some targets such as JNK2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 are downregulated during ***prion*** infection and that upregulation of the effected target by means of an activator leads to an alternative way of treating ***prion*** infections and diseases associated with ***prion*** infection.

SUMM [0154] Thus, a method was developed for regulating the production of ***prions*** either in an individual or in cells. Said methods comprise the step of administering an individual or the cells a. . .

SUMM . . . given target such as FGF-R1, Tkt, Abl, clk1, MKK7, LIMK-2, CaM-KI, and CDC 2 in order to compete with the ***prion*** infection, it is also a reasonable approach to further support said upregulation by means of an activator. Therefore, the above-mentioned. . .

SUMM . . . compounds of the general formula (I) represent a new class of pharmaceuticals highly useful for the prophylaxis and treatment of ***prion*** infections and ***prion*** diseases.

SUMM . . . general formula (I) and/or pharmaceutically acceptable salts thereof for the manufacture of a pharmaceutical formulation for prophylaxis and/or treatment of ***prion*** infections and/or

diseases induced or caused by ***prion*** infection.

SUMM [0159] As used herein the Term " ***prion*** diseases" refers to transmissible spongiform encephalopathies. This group of neurologic diseases affects humans and many species of animals causing a . . . tissue. Among other unique features, all of these diseases are associated with the accumulation of an abnormal form of the ***prion*** protein in nerve cells that eventually leads to the death of the host. While ***prion*** diseases can all be transmitted from one host to another, it remains contentious as to whether a virus-like infectious agent or the ***abnormal*** ***prion*** protein itself, the ***prion***, causes the conversion of normal to abnormal protein.

SUMM [0160] Probably most mammalian species develop ***prion*** diseases. Specific examples for animals include:

Scrapie sheep, goat

TME (transmissible mink encephalopathy): mink

CWD (chronic wasting disease):. . .

SUMM [0161] Humans are also susceptible to several ***prion*** diseases. Examples are:

CJD Creutzfeld-Jacob Disease

GSS Gerstmann-Straussler-Scheinker syndrome

FFI Fatal familial Insomnia

Kuru

Alpers Syndrome

SUMM [0162] The human ***prion*** diseases include kuru, sporadic Creutzfeldt-Jacob disease (sCJD), familial CJD (fCJD), iatrogenic CJD (iCJD), Gerstmann-Straussler-Scheinker (GSS) disease, fatal familial insomnia (FFI), and, more recently, new variant CJD (nvCJD or vCJD). In addition to these human diseases, ***prion*** -related diseases, have been recognized in several animal hosts. Scrapie is a naturally occurring disease of sheep and goats that causes ataxia, behavioral changes, and a severe pruritus that leads to scraping behavior, from which the disease was named. Additional ***prion*** diseases in animals include transmissible mink encephalopathy (TME), chronic wasting disease (CWD) of deer and elk, feline spongiform encephalopathy (FSE),.

SUMM [0163] The transmissible nature of ***prion*** disease was first demonstrated experimentally in 1936 when Cuille and Chelle transmitted scrapie to a healthy goat by the intraocular. . .

SUMM [0165] The term " ***prion*** " was coined to indicate an infectious agent with proteinlike properties. The unusual properties of the pathogen were demonstrated in early. . .

SUMM . . . PrP.sup.Sc contains at least 40% pleated sheet structure. Conversion to this sheet structure appears to be the fundamental event in ***prion*** disease. The ultimate mechanism of how cells die coincident with the generation of ***prions*** is still unclear. Simple accumulation of pathogenic protein may not be sufficient to explain disease, however, it may constitute a. . .

SUMM . . . was shown that the pyridylpyrimidine compounds of the general formula (I) are highly effective for the prophylaxis and/or treatment of ***prion*** infections and/or ***prion*** diseases selected from the group comprising Scrapie, TME, CWD, BSE, CJD, vCJD, GSS, FFI, Kuru, and Alpers Syndrome. Preferably, the. . .

SUMM [0168] The above-mentioned ***prion*** infections and/or diseases associated with ***prion*** infections can be treated using the inventive pyridylpyrimidine derivatives by targeting at least one of the human cellular protein kinases,. . .

SUMM . . . According to these findings a further aspect of the present invention is directed to a method for preventing and/or treating ***prion*** infections and/or ***prion*** diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent. . .

SUMM [0170] Another aspect is related to a method for preventing and/or treating ***prion*** infections and/or ***prion*** diseases in cells or cell cultures comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically. .

SUMM . . . Because of the fact that the targets JNK2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1 are downregulated in cells infected with ***prions***, an upregulation of said targets represents another strategy in order to treat ***prion*** infections and diseases like CJD (nvCJD or vCJD) associated with ***prion*** infections. Said upregulation can be performed by activators.

SUMM [0174] Thus, another embodiment of the present invention describes a method for preventing and/or treating ***prion*** infections and/or diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically. .

SUMM . . . convert to PrP.sup.Sc? Potential mechanisms that initiate conversion of PrP.sup.c to PrP.sup.Sc include a germ line mutation of the human ***prion*** protein gene (PRNP), a somatic mutation within a particular neuron, and spontaneous conversion of PrP.sup.c to an aberrant conformation that is not refolded appropriately to its native structure. The ***prion*** protein gene (PRNP) is the single gene on the short arm of chromosome 20 in humans which encodes the normal cellular isoform of the ***prion*** protein. Regardless of the initiating event, once an "infectious unit" has been generated, PrP.sup.Sc appears to act as a conformational. . . supported by several studies which show that mice with the normal PrP gene deleted (PrP knockout mice) do not develop ***prion*** disease after inoculation with scrapie. Furthermore, transgenic (Tg) mice that express a chimeric PrP gene made of human and mouse segments develop protease-resistant chimeric mouse-human Prp.sup.Sc in their brains when inoculated with brain extracts from humans with ***prion*** disease. These findings clearly illustrate that ***prions*** do not self-replicate but instead convert nonpathogenic PrP.sup.c to pathogenic PrP.sup.Sc.

SUMM [0180] In its sporadic or nonfamilial form, CJD is the most common of the human ***prion*** diseases. Confusion and forgetfulness which progress rapidly to severe cortical dementia in combination with ataxia, myoclonus, and an abnormal electroencephalogram. . .

SUMM . . . regionally or diffusely throughout the cortex that are immunoreactive to anti-human PrP antibodies is the hallmark of this form of ***prion*** disease.

SUMM [0186] The occurrence of vCJD is sobering because it appears to represent a situation in which the ***prion*** has "jumped" species, in this case from cow to human. Because the pathologic features and clinical presentation of vCJD differ significantly from those of sCJD, it is considered a new "strain" of human ***prion*** disease. The same "protein signature" was observed following experimental transmission of BSE to several animal hosts, supporting the idea that.

SUMM [0187] Kuru is the condition which first brought ***prion*** diseases to prominence in the 1950s. The disease was found in geographically isolated tribes in New Guinea. It was established. . .

SUMM [0188] Alpers Syndrome is the name given to ***prion*** diseases in infants.

SUMM [0197] As described above, said ***prion*** infection and/or disease

associated with said ***prion*** infection is selected from the group comprising Scrapie, TME, CWD, BSE, vCJD, CJD, GSS, FFI, Kuru, and Alpers Syndrome. Preferably, . . .

SUMM [0198] Some methods of the present invention identify compounds useful for prophylaxis and/or treatment of ***prion*** infections and/or diseases by screening a test compound, or a library of test compounds; for its ability to inhibit at . . . the above-mentioned human cellular protein kinases, phosphatases, or cellular signal transduction molecules, identified herein as characteristically up- or downregulated during ***prion*** production or growth inside a cell or individual. A variety of assay protocols and detection techniques are well known in . . .

SUMM . . . a solid support is disclosed in the present invention useful for screening compounds useful for the prophylaxis and/or treatment of ***prion*** infections and/or diseases in an individual, the solid support comprising at least one immobilized oligonucleotide, wherein said oligonucleotide encodes one. . .

SUMM . . . the present invention is related to a solid support useful for screening compounds useful for the prophylaxis and/or treatment of ***prion*** infections and/or diseases in an individual, the solid support comprising at least one immobilized human cellular protein kinase, phosphatase or. . .

SUMM . . . on a solid support. Thus, another aspect of the present invention is directed to a solid support useful for detecting ***prion*** infections and/or diseases in an individual, the solid support comprising an immobilized oligonucleotide, wherein said oligonucleotide is capable of detecting. . .

SUMM [0215] The present invention discloses also for the first time a solid support useful for detecting ***prion*** infections and/or diseases in cells, the solid support comprising an immobilized oligonucleotide, wherein said oligonucleotide is capable of detecting activity. . .

SUMM . . . Tkt, Abl, ckl1, MKK7, LIMK-2, CaM-KI, JNK2, CDC2, PRK, PTP-SL, PTP-zeta, HSP86, and GPIR-1, or which are effective to treat ***prion*** infections and diseases associated with ***prion*** infection. Said ***prion*** infections and diseases are preferably Scrapie, TME, CWD, BSE, vCJD, CJD, GSS, FFI, Kuru, and Alpers Syndrome.

SUMM [0222] Said pharmaceutical compositions are useful for the prophylaxis and/or treatment of an individual afflicted with ***prions*** comprising at least one agent capable of inhibiting and/or activating at least partially the activity, the expression, and/or the production. . .

SUMM . . . and or activate, for some period of time, one or more of the clinically defined pathological processes associated with the ***prion*** infection. The effective amount may vary depending on the specific inhibitor and/or activator selected, and is also dependent on a. . .

DRWD [0251] FIG. 1 shows 6 selected pyridylpyrimidine derivatives which are suitable inhibitors for ***prion*** diseases, namely compounds 4, 5, 37, 52, 84, and 88;

DRWD [0253] FIG. 3 shows selected compounds that have been identified as potent inhibitors in a ***prion*** propagation assay at a concentration of 5 .mu.m.

DETD . . . PrP. Residues 109 and 112 of murine PrP were replaced by methionine to introduce the epitope for reactivity with the ***monoclonal*** anti-PrP antibody 3F4. Cells were maintained in Dulbecco's modified Eagle's (DMEM) or Opti-MEM medium containing 10% fetal calf serum, antibiotics. . .

DETD . . . the enhanced chemiluminescence blotting kit from Amersham Corporation. Specific immuno-staining of the PrP.sup.c and PrP.sup.Sc forms were obtained with the ***prion*** protein specific antibody 3F4 (Signet Pathologies, U.S.A.).

DETD [0279] Determination of the amount of the pathogenic form of the ***prion*** protein PrP^{sup}.Sc upon treatment of ***prion*** infected cells with different types of small molecule protein kinase inhibitors resulted in the identification of a compound class of. . .

DETD [0280] These compounds significantly reduced the amount of PrP^{sup}.Sc in ***prion*** infected cells in a concentration range between 5 and 20 .mu.M (final concentration). As shown in FIG. 3 the selected compounds 4, 5, 37, and 53 inhibit almost completely the activity of ***prion*** propagation within said concentration range.

DETD . . . on the cells in these concentrations. Therefore these molecules described herein serve as potential inhibitors for the medical intervention of ***prion*** diseases such as transmissible spongiform encephalitis (TSE) infections which include Bovine spongiform encephalitis (BSE) or the new variant of Creutzfeld. . .

CLM What is claimed is:

4. Use of a compound according to claim 2 or 3 for the prophylaxis and/or treatment of ***prion*** infections and/or diseases induced by ***prion*** infection.

. . . of claims 2-9 and/or pharmaceutically acceptable salts thereof for the manufacture of a pharmaceutical composition for prophylaxis and/or treatment of ***prion*** infections and/or diseases induced by ***prion*** infection and/or neurodegenerative diseases.

11. Use according to claim 4 or 10 wherein said ***prion*** infection and/or disease is selected from the group comprising Scrapie, TME, CWD, BSE, CJD, vCJD, GSS, FFI, Kuru, and Alpers. . .

12. Use according to claim 11 wherein said ***prion*** infection is BSE, vCJD, or CJD.

17. Method for preventing and/or treating ***prion*** infections and/or ***prion*** diseases induced by ***prion*** infections in an individual which comprises administering to the individual an amount of at least one compound recited in any one of claims 3 to 8 and/or pharmaceutically acceptable salts thereof effective to prevent and/or treat said ***prion*** infection and/or disease.

18. Method for preventing and/or treating ***prion*** infections and/or ***prion*** diseases induced by ***prion*** infections in an individual which comprises administering to the individual an amount of at least one compound recited in claim 8 and/or pharmaceutically acceptable salts thereof effective to prevent and/or treat said ***prion*** infection and/or disease.

19. Method for detecting ***prion*** infections and/or ***prion*** diseases in an individual comprising: a) providing a sample from said individual; b) adding to said sample a pharmaceutically effective. .

21. Method for detecting ***prion*** infections and/or ***prion*** diseases in cells, cell cultures and/or cell lysates comprising: a) providing said cells, cell cultures and/or cell lysates; b) adding. .

22. Method for preventing and/or treating ***prion*** infections and/or ***prion*** diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent. . .

23. Method for preventing and/or treating ***prion*** infections and/or ***prion*** diseases in cell or cell cultures comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically. . .

24. Method for regulating the production of ***prions*** in an

individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which. .

.
25. Method for regulating the production of ***prions*** in cells comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically active agent which inhibits. . .

26. A ***monoclonal*** or polyclonal antibody that binds to a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from. . .

27. Method according to any one of claims 19-25, wherein the agent is a ***monoclonal*** or polyclonal antibody which binds to a human cellular protein kinase, phosphatase or a cellular signal transduction molecule selected from. . .

31. Method for detecting compounds useful for the prophylaxis and/or treatment of ***prion*** infections and/or diseases comprising: a) contacting a test compound with at least one human cellular protein kinase, phosphatase or cellular. . .

32. Method for preventing and/or treating ***prion*** infections and/or diseases in an individual comprising the step of administering a pharmaceutically effective amount of at least one pharmaceutically. .

.
33. Method for regulating the production of ***prions*** in an individual comprising the step of administering an individual a pharmaceutically effective amount of at least one pharmaceutically active. . .

34. Method for regulating the production of ***prions*** in cells comprising the step of administering the cells a pharmaceutically effective amount of at least one pharmaceutically active agent. . .

40. Method according to any one of claims 17, 18, 19, 21, 22, 23, 31, or 32 wherein said ***prion*** infection and/or ***prion*** disease is selected from the group comprising Scrapie, TME, CWD, BSE, vCJD, CJD, GSS, FFI, Kuru, and Alpers Syndrome.

41. Method according to claim 40 wherein said ***prion*** infection and/or ***prion*** disease is BSE, vCJD, or CJD.

42. A solid support useful for detecting ***prion*** infections and/or diseases in an individual, the solid support comprising an immobilized oligonucleotide, wherein said oligonucleotide is capable of detecting. . .

43. A solid support useful for detecting ***prion*** infections and/or diseases in cells, the solid support comprising an immobilized oligonucleotide, wherein said oligonucleotide is capable of detecting activity. . .

44. A solid support useful for screening compounds useful for the prophylaxis and/or treatment of ***prion*** infections and/or diseases in an individual, the solid support comprising at least one immobilized oligonucleotide, wherein said oligonucleotide encodes one. . .

. . .
45. A solid support useful for screening compounds useful for the prophylaxis and/or treatment of ***prion*** infections and/or diseases in an individual, the solid support comprising at least one immobilized human cellular protein kinase, phosphatase or. . .

46. Composition useful for the prophylaxis and/or treatment of an individual afflicted with ***prions*** comprising at least one agent capable of inhibiting at least partially the activity of at least one human cellular protein. . .

47. Composition useful for the prophylaxis and/or treatment of an individual afflicted with ***prions*** comprising at least one agent capable of activating or stimulating at least partially the activity of at least one human. . .

L12 ANSWER 16 OF 23 USPATFULL on STN
 AN 2003:232025 USPATFULL
 TI Ligands specific for an isoform of the ***prion*** protein
 IN James, William Siward, Oxford, UNITED KINGDOM
 Hope, James, Newbury, UNITED KINGDOM
 Tahiri-Alaoui, Abdessamad, Oxford, UNITED KINGDOM
 PI US 2003162225 A1 20030828
 AI US 2002-295798 A1 20021115 (10)
 RLI Continuation of Ser. No. WO 2001-GB2228, filed on 18 May 2001, UNKNOWN
 PRAI GB 2000-12054 20000518
 DT Utility
 FS APPLICATION
 LREP GRAY CARY WARE & FREIDENRICH LLP, 4365 EXECUTIVE DRIVE, SUITE 1100, SAN
 DIEGO, CA, 92121-2133
 CLMN Number of Claims: 10
 ECL Exemplary Claim: 1
 DRWN 10 Drawing Page(s)
 LN.CNT 1030
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB ***Prion*** protein, PrP, ligands are provided, especially protease
 resistant and nuclease resistant ligands. Ligands selective for isoforms
 such as PrP.sup.SC can be prepared. In a related aspect, the PrP ligands
 are used in diagnostic tests for PrP. The ligands also have potential
 for a role in the development of therapeutic methods for treatment of
 TSEs.
 TI Ligands specific for an isoform of the ***prion*** protein
 AB ***Prion*** protein, PrP, ligands are provided, especially protease
 resistant and nuclease resistant ligands. Ligands selective for isoforms
 such as PrP.sup.SC can. . .
 SUMM [0001] The present invention relates to ligands. More particularly the
 invention relates to ligands for ***prion*** proteins.
 SUMM . . . disease (CJD), variant CJD (vCJD), bovine spongiform
 encephalopathy (BSE) and scrapie, are characterized by the accumulation
 of aggregates of the ***abnormal*** ***prion*** protein
 (PrP.sup.SC) in the brain and other infected tissues.sup.1,2. The normal
 form, PrP.sup.C, which is dominated by .alpha.-helices towards the. .
 SUMM . . . difficult to study and so the development of selective ligands
 for the different isoforms would provide invaluable tools for studying
 prion disease pathogenesis. In addition, reagents that were able
 to bind PrP.sup.SC with high affinity but were less able to bind. . .
 SUMM . . . a PrP ligand of the appropriate selectivity, despite strenuous
 efforts using PrP knockout mice as recipients.sup.10 and phage-display
 technology.sup.11. A ***monoclonal*** antibody, 15B3, described by
 Oersch.sup.12 has not yet been made widely available and so must still
 be considered unproven. More. . .
 SUMM . . . under conditions appropriate for binding of the ligand to the
 prior protein. Optionally, the binding of the ligand to the
 prion protein and/or the absence of binding of proteins other
 than the desired PrP to the ligand may be detected.
 SUMM [0027] Aptamers with this motif are preferred, especially
 monoclonal aptamers.
 SUMM [0030] In one embodiment, we provide ligands that can discriminate
 between normal and disease isoforms of the ***prion*** protein
 (PrP). In particular, we have isolated 2'-F nucleic acid ligands, or
 aptamers, to the abnormal PrP isoform derived from. . .
 SUMM [0047] Cloning and Sequencing of ***Monoclonal*** Aptamers
 SUMM . . . ABI (Perkin-Elmer). The resulting sequences were compared to
 each other and aligned using ClustalX (version 1.64B). Four
 representative 2'-F RNA ***monoclonal*** aptamers were selected for

further analysis; these were aptainers 73, 76, 90 and 93.

SUMM [0049] 5' End Labeling of ***Monoclonal*** Aptamers

SUMM [0050] PCR-amplified templates for ***monoclonal*** aptamers 73, 76, 90 and 93 were in vitro transcribed as described above. The reactions were incubated overnight at 37.degree. . . .

SUMM [0051] To label 2'-F RNA ***monoclonal*** aptamers at the 5' terminus, transcripts were dephosphorylated using bacterial alkaline phosphatase (Pharmacia-Amersham Biotech), incubated in presence of [γ-.sup.32P] ATP. . . equal volume of formamide stop buffer and resolved on a 10% denaturing polyacrylamide gel in TBE buffer. Labeled 2'-F RNA ***monoclonal*** aptamers were visualized by autoradiography, excised from the gel, eluted and precipitated as described above. The purified 2'-F RNA ***monoclonal*** aptamers were dissolved in water, quantified by Cerenkov counting and used for gel mobility shift, footprinting and structural analysis.

SUMM [0052] Affinity and Specificity of ***Monoclonal*** Aptamers for Recombinant Bovine PrP

SUMM [0055] Nuclease Mapping of ***Monoclonal*** 2'-F Aptamers and Footprinting

SUMM . . . analysed by agarose gel electrophoresis. Parallel samples of the human and animal brain homogenates were analysed by western blotting using ***monoclonal*** antibody 6H4. This confirmed the presence of PrP.sup.Sc only in the case of individuals with TSE (data not shown).

DRWD [0069] FIG. 2. Affinity and specificity of ***monoclonal*** aptamers for recombinant bovine PrP

DRWD [0070] A. Example of band shift affinity analysis of ***monoclonal*** aptamers against recombinant bovine PrP. 5000 c.p.m. (about 0.01 pmol) of .sup.32P-labelled aptamer 73 was mixed with recombinant bovine PrP.

DRWD . . . shows the autoradiograph revealing the position of aptamer and aptamer-PrP complexes. The right hand panel shows a parallel immunoblot, using ***monoclonal*** anti-PrP antibody 6H4 to detect the presence of PrP and PrP-containing complexes.

DRWD . . . shows the autoradiograph revealing the position of aptamer and aptainer-PrP complexes. The right hand panel shows a parallel immunoblot, using ***monoclonal*** anti-PrP antibody 6H4 to detect the presence of PrP and PrP-containing complexes.

DETD [0099] Affinity and Specificity of ***Monoclonal*** Aptamers for Recombinant Bovine PrP

DETD . . . interested in isolating aptamers that would be able to analyse PrP isolated from multiple species, we screened the in vitro-transcribed, ***monoclonal*** sequences against recombinant bovine PrP. We found that they all bound to bovine PrP in a concentration-dependent manner (see, for. . . .

DETD . . . aptamers, those we describe here have substantially higher affinity for the .beta.-form of PrP than for its .alpha.-isoform. Although one ***monoclonal*** antibody has been described that has a greater affinity for aggregated PrP compared to the normal isoform of the protein. . . .

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L12 ANSWER 17 OF 23 USPATFULL on STN

AN 2003:213736 USPATFULL

TI Anti-abnormal type ***prion*** ***monoclonal*** antibody, process for producing the same, and immunoassay using the same

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PI US 2003148374 AI 20030807

AI US 2001-5120 AI 20011207 (10)

DT Utility

FS APPLICATION

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CLMN Number of Claims: 17

ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)

LN.CNT 567

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A ***monoclonal*** antibody which enables to distinguish the abnormal type ***prion*** from the normal type ***prion***, as well as production process thereof, is disclosed. The anti-abnormal type ***prion*** ***monoclonal*** antibody of the invention reacts with abnormal type ***prion*** by antigen-antibody reaction but does not substantially react with normal type ***prion*** by antigen-antibody reaction. The anti-abnormal type ***prion*** ***monoclonal*** antibody of the invention may be obtained by immunizing an animal with an immunogen including a peptide containing a plurality of regions in the abnormal type ***prion***, which regions are discontinuous each other in primary amino acid sequence of the abnormal type ***prion***

TI Anti-abnormal type ***prion*** ***monoclonal*** antibody, process for producing the same, and immunoassay using the same

AB A ***monoclonal*** antibody which enables to distinguish the abnormal type ***prion*** from the normal type ***prion***, as well as production process thereof, is disclosed. The anti-abnormal type ***prion*** ***monoclonal*** antibody of the invention reacts with abnormal type ***prion*** by antigen-antibody reaction but does not substantially react with normal type ***prion*** by antigen-antibody reaction. The anti-abnormal type ***prion*** ***monoclonal*** antibody of the invention may be obtained by immunizing an animal with an immunogen including a peptide containing a plurality of regions in the abnormal type ***prion***, which regions are discontinuous each other in primary amino acid sequence of the abnormal type ***prion***

SUMM [0002] The present invention relates to an anti-abnormal type ***prion*** ***monoclonal*** antibody, process for producing the same, and immunoassay of abnormal type ***prion*** using the same.

SUMM . . . system, and progressively aggravate to death. Although the cause of the diseases has not been fully clarified, the so called " ***prion*** hypothesis" which assumes that the diseases are not caused by infectious pathogen such as a virus, but are caused by deposition of abnormal type ***prion*** protein, is now believed by most of the researchers. These diseases are diagnosed by pathological analysis of thin section of. . .

SUMM [0006] Normal ***prion*** protein is a glycoprotein existing in cell membranes, which widely occurs in various eukaryotes such as yeasts. The gene encoding normal ***prion*** is a single gene and the encoded amino acid sequence is very well conserved among the mammals. Especially, it has. . .

SUMM [0007] Although the function of the normal type ***prion*** protein has not yet been clarified, since the amino acid sequence is well conserved, it is presumed that it plays an important role in generation, development and function of nerve tissue. With a knock out mouse in which the ***prion*** gene is knocked out, abnormal walking such as shaking of the lower half of the body with aging, and pathologically,

SUMM [0008] In human, although variations in a part of the amino acid sequence (primary structure) of the ***prion*** protein among individuals have been reported, there is no difference between the amino acid sequences of ***prion*** protein in CJD patients and normal individuals. Therefore, it is thought that deposition of the ***abnormal*** ***prion*** protein is not because of the amino acid sequence, but because of the difference in stereostructure. Therefore, the conventional anti- ***prion*** antibodies which recognize the primary amino acid sequence of ***prion*** cannot distinguish the abnormal type ***prion*** from the normal type ***prion***. Further, since the amino acid sequence is well conserved between animals, it is presumed that antigenicity of ***prion*** is low. Thus, production of an anti-abnormal type ***prion*** antibody using an immunogen keeping the stereostructure thereof, in which the antigenicity of the immunogen is increased, is demanded.

SUMM [0009] An object of the present invention is to provide a ***monoclonal*** antibody which can distinguish the abnormal type ***prion*** from the normal type ***prion***, as well as a production process thereof. Another object of the present invention is to provide an immunoassay of the abnormal type ***prion*** using the ***monoclonal*** antibody.

SUMM [0010] It is thought that a ***monoclonal*** antibody which can distinguish the abnormal type ***prion*** from the normal type ***prion*** may be obtained by immunizing an animal with the abnormal type ***prion***, obtaining ***monoclonal*** antibodies by a conventional method, and by screening a ***monoclonal*** antibody which reacts with the abnormal type ***prion*** but does not react

with the normal type ***prion***. However, not only because of the fact that there are no differences in the amino acid sequence of the normal. . . the low species specificity, it is difficult to induce an antibody, especially an antibody which can distinguish the abnormal type ***prion*** from the normal type ***prion***. Further, abnormal type ***prion*** is a protein which is difficult to obtain in a sufficient amount for use as an immunogen. The frequency of the diseases yielding abnormal type ***prion*** is low, and the facilities which can deal with the abnormal type ***prion*** are limited because it is a strong pathogen. Because of these, it is difficult to obtain the abnormal type ***prion*** in a large amount. Further, to use the abnormal type ***prion*** protein as an immunogen, it is necessary to purify the protein to some degree. However, the protein is insolubilized in. . . to the abnormal type be kept during the solubilization step. Because of these reasons, it is difficult to prepare a ***monoclonal*** antibody which can distinguish the abnormal type ***prion*** from the normal type ***prion***.

SUMM [0011] The present inventors intensively studied to locate the exposed regions in the stereostructure of the abnormal type ***prion***, and to succeed in preparing a ***monoclonal*** antibody which can distinguish the abnormal type ***prion*** from the normal type ***prion***, thereby completing the present invention.

SUMM [0012] That is, the present invention provides an anti-abnormal type ***prion*** ***monoclonal*** antibody which reacts with abnormal type ***prion*** but does not substantially react with normal type ***prion*** by antigen-antibody reaction, or an antigen-binding fragment thereof. The present invention also provides a hybridoma which produces the ***monoclonal*** antibody according to the present invention. The present invention further provides a method for measuring abnormal type ***prion*** by an immunoassay utilizing the antigen-antibody reaction between the ***monoclonal*** antibody according to the present invention and an abnormal type ***prion***. The present invention still further provides an immunoassay kit for carrying out the immunoassay of the present invention, comprising the ***monoclonal*** antibody or the antigen-binding fragment thereof according to the present invention. The present invention still further provides process for producing the anti-abnormal type ***prion*** ***monoclonal*** antibody according to the present invention, comprising immunizing an animal with an immunogen including a peptide containing a plurality of regions in said abnormal type ***prion***, which regions are discontinuous each other in primary amino acid sequence of said abnormal type ***prion***; preparing hybridomas originated from antibody-producing cells of the immunized animal; screening a hybridoma which produces an anti-abnormal type ***prion*** ***monoclonal*** antibody which reacts with the abnormal type ***prion*** but does not substantially react with the normal type ***prion*** by antigen-antibody reaction; and recovering said anti-abnormal type ***prion*** ***monoclonal*** antibody from the hybridoma selected by the screening. The present invention still further provides an immunogen used in the above-mentioned process for producing the ***monoclonal*** antibody of the present invention.

SUMM [0013] By the present invention, an anti-abnormal type ***prion*** ***monoclonal*** antibody which reacts with abnormal type ***prion*** but does not substantially react with normal type ***prion*** by antigen-antibody reaction, or an antigen-binding fragment thereof was first provided. As a result, immunoassay of the abnormal type ***prion*** was first attained. Thus, the present invention will make a great contribution to the diagnosis of bovine and other animals. . .

DRWD [0014] FIG. 1 schematically shows the stereostructure of the abnormal type ***prion*** described in Korth et al., and the stereostructure

of the abnormal type ***prion***, which was presumed by the present inventors.

DETD [0015] The ***monoclonal*** antibody according to the present invention reacts with the abnormal type ***prion*** by antigen-antibody reaction but does not substantially react with the normal type ***prion***. The term "does not substantially react" means that the immunological reactivity with the normal type ***prion*** is lower than the immunological reactivity with the abnormal type ***prion*** to a discernable degree. Thus, even if a ***monoclonal*** antibody has a cross-reactivity with the normal type ***prion***, in case where the affinity to the normal type ***prion*** is lower than the affinity to the abnormal type ***prion*** to a discernable degree, the ***monoclonal*** antibody is included within the definition of "does not substantially react with the normal type ***prion***", and is included in the scope of the present invention. Needless to say, a ***monoclonal*** antibody which does not have a cross-reactivity with the normal type ***prion***, that is, a ***monoclonal*** antibody which reacts with the abnormal type ***prion*** but does not react with the normal type ***prion*** is preferred.

DETD [0016] The ***monoclonal*** antibody of the present invention is preferably one which reacts with the abnormal type ***prion*** but does not react with the normal type ***prion*** in immunohistostaining. In the conventional immunohistostaining for staining ***prion***, the so called "acid-autoclave treatment" (i.e., the tissue is immersed in HCl solution with a concentration of 1.0 to 100. . . mM and then autoclaved at 121.degree. C. for 20 minutes) is performed and then the immunohistostaining is carried out. The ***monoclonal*** antibody according to the present invention is preferably one which reacts with the abnormal type ***prion*** existing in the tissue which was not subjected to a pretreatment such as the acid-autoclave treatment. Examples of such an anti-abnormal type ***prion*** ***monoclonal*** antibody include the ***monoclonal*** antibody produced by hybridoma EBEB4C3Ebb. The hybridoma EBEB4C3Ebb has been deposited with National Institute of Advanced Industrial Science and Technology. . .

DETD [0017] The present invention also provides antigen-binding fragments of the above-described ***monoclonal*** antibody according to the present invention. The term "antigen-binding fragment" herein means fragment such as Fab fragment or F(ab').sub.2 fragment of the antibody, which exhibits antigen-binding property of the antibody. These fragments may easily be obtained by cleaving the ***monoclonal*** antibody of the present invention with papain or pepsin according to a conventional method. These antigen-antibody fragments may be used in the immunoassays described below equally as the ***monoclonal*** antibody of the present invention.

DETD [0018] As mentioned above, it is difficult to prepare a ***monoclonal*** antibody which reacts with the abnormal type ***prion*** but does not substantially react with the normal type ***prion*** by using the abnormal type ***prion*** as an immunogen. To solve this problem, the present inventors originally presumed the stereostructure of the abnormal type ***prion***. FIG. 1 shows the stereostructure of the normal ***prion*** (PrP.sup.C model), the stereostructure of the abnormal type ***prion*** presumed by Korth et al. (PrP.sup.SC model 1, C. Korth et al., Nature 390:74-77, 1997), and the stereostructure of the abnormal type ***prion*** PrP.sup.SC model 2) presumed by the present inventors. The stereostructure of the abnormal type ***prion***, which was presumed by the present inventors, contains more .beta. sheet structures than in the stereostructure presumed by Korth et. . . structure are: .alpha. helix 5.6%, and .beta. structure 18%. Aside from the precision of the

prediction of the secondary structure, ***prion*** protein is a protein which likely adopts .beta. structure rather than .alpha. helix. Looking into more detail, about the half. . .

DETD [0020] The present inventors thought that a ***monoclonal*** antibody which specifically reacts with the abnormal type ***prion*** may be obtained by using a peptide as an immunogen, which peptide consists essentially of the ligation of at least. . . the group consisting of B 1 region (the 128th to 131st amino acid in the primary amino acid sequence of ***prion***, hereinafter indicated as "128-131 a.a.", other regions being indicated in the same way), B2 region (138-141 a.a.), B3 region (149-152 a.a.), E1. . . a peptide (SEQ ID NO:2) which comprises the E2 region, which peptides are bound to the same KLH molecule, the ***monoclonal*** antibody produced by the above-mentioned hybridoma EBEB4C3Ebb was obtained. The above-described regions may be directly ligated or indirectly ligated by. . .

DETD [0027] The ***monoclonal*** antibody according to the present invention may be prepared by a conventional method except that the above-described immunogen is used.. . immunogen, and hybridomas derived from antibody-producing cells of the immunized animal are prepared. The hybridomas are screened for those producing ***monoclonal*** antibodies which react with the abnormal type ***prion*** and does not substantially react with the normal type ***prion***, and the desired ***monoclonal*** antibody is recovered from the screened hybridoma. The method for preparing hybridomas by fusing antibody-producing cells such as spleen cells. .

DETD [0028] By an immunoassay utilizing the antigen-antibody reaction between the ***monoclonal*** antibody according to the present invention and the abnormal type ***prion***, the abnormal type ***prion*** may be measured. The term "measure" herein includes both detection and quantitation. The immunoassays per se are well-known in the. . .

DETD . . . so it is not necessary to explain these immunoassays in the present specification. Briefly, in sandwich immunoassays, for example, the ***monoclonal*** antibody or an antigen-binding fragment thereof is immobilized on a solid support as a first antibody. The first antibody is. . . after washing the solid support, the resultant is then reacted with a second antibody which reacts with the abnormal type ***prion*** by antigen-antibody reaction (the second antibody may be an antibody which also reacts with the normal type ***prion***, and may be either a ***monoclonal*** antibody or a polyclonal antibody). After washing the solid support, the second antibody bound to the solid support is measured.. . The above-mentioned measurement is conducted for a plurality of standard samples each containing a known concentration of the abnormal type ***prion***, and the relationship between the concentrations of the abnormal type ***prion*** in the standard samples and the measured amounts of the label is plotted to prepare a calibration curve. The abnormal type ***prion*** in a test sample may be determined by applying the measured amount to the calibration curve. It should be noted that the above-mentioned first antibody and the above-mentioned second antibody may be exchanged. In agglutination immunoassays, the ***monoclonal*** antibody according to the present invention or an antigen-binding fragment thereof is immobilized on particles such as latex particles, and. . . The above-mentioned measurement is conducted for a plurality of standard samples each containing a known concentration of the abnormal type ***prion***, and the relationship between the concentrations of the abnormal type ***prion*** in the standard samples and the measured absorbance is plotted to prepare a calibration curve. The abnormal type ***prion*** in a test sample may be determined by applying the measured absorbance to the calibration curve.

DETD [0030] The reagents necessary for each type of immunoassay are also

well-known in the art. Except for the ***monoclonal*** antibody used, the immunoassay according to the present invention may be carried out using an ordinary kit for immunoassay. For. . .

DETD [0033] Korth et al. analyzed the epitope of the bovine ***prion*** protein by using a recombinant antigen expressed by a genetic recombination technique, and reported that the major antigenic regions of the ***prion*** protein are the above-mentioned three regions, i.e., E1, E2 and E3 regions (Korth et al., supra). In the stereostructure of the normal type ***prion*** expected from these results, E2 and E3 regions are close, but E1 region is apart from E2 and E3 regions.. . .

DETD [0037] (3) Screening of ***Monoclonal*** Antibodies Which Specifically Reacts with Abnormal Type ***Prion*** .

DETD . . . acid-autoclave treatment and not subjected to this pretreatment were used, and antibody clones which specifically reacts with the abnormal type ***prion*** protein were selected. As a control, thin sections of brain from normal human, which were subjected to the acid-autoclave treatment. . .

DETD . . . treatment was performed, and the symbol "-" means that the acid-autoclave treatment was not performed. In the line of each ***monoclonal*** antibody, the symbol means positive, the symbol "-" means negative, and the symbol "+.sup.W" means weakly positive.)

DETD [0057] As shown, ***monoclonal*** antibodies which react with the abnormal type ***prion*** but do not react with the normal type ***prion***, which enable to distinguish the abnormal type ***prion*** from the normal type ***prion***, were obtained. The hybridoma EBEB4C3Ebb which produces such a ***monoclonal*** antibody has been deposited with National Institute of Advanced Industrial Science and Technology under the Budapest Treaty under an accession. .

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 1

LENGTH: 15

TYPE: PRT

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Peptide used as immunogen for raising anti-
abnormal ***prion*** ***monoclonal*** antibody

SEQUENCE: 1

Ile Ile His Phe Ser Asp Tyr Glu Asp Arg Tyr Tyr Arg Glu

1 . . . 5 . . .

DETD SEQUENCE CHARACTERISTICS:

SEQ ID NO: 2

LENGTH: 12

TYPE: PRT

ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Peptide used as immunogen for raising anti-
abnormal ***prion*** ***monoclonal*** antibody

SEQUENCE: 2

Val Tyr Tyr Arg Pro Met Asp Glu Tyr Ser Asn Cys

1 . . . 5 . . . 10 . . .

CLM What is claimed is:

1. An anti-abnormal type ***prion*** ***monoclonal*** antibody which reacts with abnormal type ***prion*** but does not substantially react with normal type ***prion*** by antigen-antibody reaction, or an antigen-binding fragment thereof.

2. The ***monoclonal*** antibody or the antigen-binding fragment thereof according to claim 1, which reacts with said abnormal type ***prion*** and does not substantially react with said normal type

prion in immunohistostaining.

3. The ***monoclonal*** antibody or the antigen-binding fragment thereof according to claim 1 or 2, which reacts with said abnormal type ***prion*** which was not subjected to pretreatment.

4. The ***monoclonal*** antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, originated from an animal immunized. . .

5. A ***monoclonal*** antibody or the antigen-binding fragment thereof, which is produced by hybridoma EBEB4C3Ebb (FERM BP-7808).

6. The ***monoclonal*** antibody or the antigen-binding fragment thereof according to any one of claims 1 to 5, which is a ***monoclonal*** antibody.

7. A hybridoma which produces the ***monoclonal*** antibody according to any one of claims 1 to 5.

8. A method for measuring abnormal type ***prion*** by an immunoassay utilizing said antigen-antibody reaction between said ***monoclonal*** antibody according to any one of claims 1 to 6, and an abnormal type ***prion*** .

9. An immunoassay kit for carrying out the method of claim 8, comprising the ***monoclonal*** antibody or the antigen-binding fragment thereof according to any one of claims 1 to 6.

10. A process for producing the anti-abnormal type ***prion*** ***monoclonal*** antibody according to any one of claims 1 to 6, comprising immunizing an animal with an immunogen including a peptide consisting essentially of a plurality of regions in said abnormal type ***prion*** , which regions are discontinuous each other in primary amino acid sequence of said abnormal type ***prion*** , and which regions are ligated each other in said peptide; preparing hybridomas originated from antibody-producing cells of the immunized animal; screening a hybridoma which produces an anti-abnormal type ***prion*** ***monoclonal*** antibody which reacts with said abnormal type ***prion*** by antigen-antibody reaction but does not substantially react with said normal type ***prion*** by antigen-antibody reaction; and recovering said anti-abnormal type ***prion*** ***monoclonal*** antibody from said hybridoma selected by said screening.

16. The anti-abnormal type ***prion*** ***monoclonal*** antibody which was produced by the process according to any one of claims 10 to 15.

L12 ANSWER 18 OF 23 USPATFULL on STN

AN 2003:30309 USPATFULL

TI Methods and compositions for detection of disease

IN Ramberg, Elliot R., Del Ray Beach, FL, UNITED STATES

PI US 2003022256 A1 20030130

AI US 2001-776568 A1 20010202 (9)

PRAI US 2000-179668P 20000202 (60)

US 2000-183377P 20000218 (60)

US 2000-218879P 20000718 (60)

DT Utility

FS APPLICATION

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CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 7 Drawing Page(s)

LN.CNT 2159

AB The present invention is directed to methods and compositions for detection of target analytes, comprising proteins and nucleic acids, in multiple cellular compartments. Preferred embodiments comprise the use of complement-mediated assays. Methods and compositions for monitoring multiple stages of disease and infection are presented.

SUMM [0011] Other attempts at measuring infectious agents include the tests for ***prions***. Creutzfeld-Jakob disease (CJD) of humans and bovine spongiform encephalitis (BSE) and scrapie of animals are neurodegenerative diseases caused by ***prion*** proteins. The infectious ***prion*** is an abnormal disease-producing isoform of the normal ***prion*** protein (PrP) called PrP^{sup.sc}. Brain damage in ***prion*** disease occurs when ***abnormal*** ***prion*** protein molecules, as a consequence of ingestion gain entry to the brain and cause normal PrPs to take on the. . .

SUMM [0012] Currently a labeled mouse ***monoclonal*** antibody 3F4 has been shown to bind ***prions*** with a sensitivity of binding of the antibody of 5 picograms per ml. This indicates that billions of ***prion*** protein molecules or greater would be necessary to be present to support detection of binding of the antibody to the aberrant ***prion***. Furthermore, the assay is complex, requiring selective precipitation of PrP^{sup.sc} by sodium phosphotungstate. This inability to more sensitively detect the presence of the ***prions*** in TSEs has hampered an understanding of the disease, attempts to determine if a cure scenario is feasible, and development. . .

SUMM . . . the protein in a large sample of plasma and concentrate and collect the normal and the aberrant forms of the ***prion*** in a small volume. Furthermore, methods are needed for diagnostic assays that will detect the presence of the aberrant ***prion*** protein with high levels of sensitivity.

SUMM . . . of detection. CMSA comprises the fixation and activation of complement by interactions between cell subset specific surface membrane proteins, and ***monoclonal*** or other antibodies. The initiation of the complement fixation process results in the production of the C3a peptide in quantities. . .

DETD . . . comprises CMSA. CMSA comprises the fixation and activation of complement by interactions between cell subset specific surface membrane proteins, and ***monoclonal*** or other antibodies. The initiation of the complement fixation process results in the production of the C3a peptide in quantities. . .

DETD . . . shown in FIGS. 1 to 6. Herein, the intact cell, or cell membrane ghost, or nucleus is treated with a ***monoclonal*** antibody specific for a surface protein of interest, thereby forming an Ab/Ag complex that fixes complement. In the presence of. . . (FIG. 4) or may also be a cell membrane or cell nucleus, as well as an immunogenic carcinogen or pathologic ***prion*** protein molecule.

DETD . . . C3a peptides are produced due to the interactive presence of a lipid membrane containing a unique surface protein (immunogen), a ***monoclonal*** or polyclonal antibody, and the complement cascade components. The presence and quantification of the C3a peptide produced may be achieved. . .

DETD . . . the extent of complement fixation and activation. The cell surface membrane and nuclear membrane protein markers react with the specific ***monoclonal*** or other antibody to the immunogens resulting in fixation and activation of complement. Also cell surface polysaccharides and other materials. . .

DETD . . . The extent of complement fixation and activation is influenced by many factors. These factors include avidity of the epitope and

monoclonal antibody, and concentration of key intermediates in the complement cascade. For example, spiking native complement with additional C3 will increase. . .

DETD . . . the present invention comprises using a peptide with many epitopes that affords multiple Ag/Ab (antigen/antibody) reactions by use of a ***monoclonal*** antibody cocktail, with each antibody being specific to a different epitope on a single reporter probe. This results in fixation. . .

DETD . . . more preferably each IgG antibody has a different specificity. For example, one IgG of the pair is an IgG anti-Rh ***monoclonal*** antibody used to attach the antibody pair to the RBC surface, without any need for chemical modification of the RBC. The second IgG of the pair is an IgG anti-epitope ***monoclonal*** antibody used to bind the epitope present on the reporter probe and to fix and activate complement.

DETD . . . of pathologic nuclei and cell membrane ghosts. Surface protein markers are detected by their reaction with specific IgG or other ***monoclonal*** antibodies. Though ***monoclonal*** antibodies are used herein, it is contemplated by the present invention that any type of antibody or antibody fragment that. . .

DETD . . . anti-specific ICP antibodies, that will only react with the free-floating ICPs in solution. In this embodiment RBCs linked to anti-ICP ***monoclonal*** antibodies will in the presence of complement undergo complement-mediated immunoerythrocyte lysis, releasing hemoglobin for quantitation.

DETD . . . include but are not limited to, Ki-67 (MIB-1); Cdc, McM antigens: NMP(CvC-3); HMGI (Y); PCNA; and Topoisomerase II Alpha markers. ***Monoclonal*** antibodies to these markers can be used in this part of the screen. Such embodiments of the present invention, termed. . .

DETD . . . this marker another surface marker can be used in conjunction to lyse the cancerous pathologic cell. Upon reaction of the ***monoclonal*** IgG anti-.beta.2 microglobulin with the exfoliative cell sample, surface antigen/antibody complexes form, fix complement, and ultimately lyse all the cells. . .

DETD . . . all cells present are mixed with mixtures of magnetic beads. Each magnetic beads grouping is coated with a single IgG ***monoclonal*** antibody or antibodies to an early dysplasia marker in panel A, thereby producing a magnetic bead cocktail. This permits the. . .

DETD [0223] MACMSA requires the presence of an antigenic epitope on the carcinogen molecule and a ***monoclonal*** antibody specific to this epitope, both currently available for the AFB1 molecule. This interaction (antigen/antibody complex) fixes and activates complement,. . .

DETD . . . Flow through supernate containing any C3a peptides generated is added to magnetic beads coated with the IgG anti C3a capture ***monoclonal*** antibody

DETD [0235] STEP VIII: Add IgG anti-C3a reporter ***monoclonal*** antibody conjugated with Alkaline phosphatase polymer and mix

DETD . . . 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK), along with the AFB1. The sole requirements are that the carcinogen possesses an immunogenic epitope and that a ***monoclonal*** or polyclonal antibody is available for use that has specificity for it.

Interestingly, all these and other carcinogens and teratogens. . .

DETD . . . VIII: Flow through supernate containing any C3a peptides generated is added to magnetic beads coated with IgG anti C3a capture ***monoclonal*** antibody and mixed

DETD [0251] STEP X: Add IgG anti C3a reporter ***monoclonal*** antibody conjugated with alkaline phosphatase polymer and mix

DETD . . . VI: Flow through supernate containing any C3a peptides

generated is added to magnetic beads coated with IgG anti C3a capture
 monoclonal antibody and mixed

DETD [0262] STEP VIII: Add IgG anti C3a reporter ***monoclonal***
 antibody conjugated with Alkaline phosphatase polymer and mix.

DETD . . . separate isolation of all B-cells, and separate isolation of
 all monocytes, by using magnetic beads coated with cell subset specific
 monoclonal antibodies, to achieve separation of non-HIV
 susceptible cell types and compartmentalization of HIV susceptible cell
 subsets.

DETD . . . cell subset analysis by first, separating the component parts
 of each cell subset as described, herein, and next using the
 monoclonal antibodies to the markers of infection listed in
 Table VIII to assess the presence of the virus and the infectious. . .

DETD . . . cells of the peripheral blood. Isolation of a very large number
 of peripheral blood nucleated cells (PBNCs) and use of
 monoclonal antibody specific to this surface HIV marker
 expressed during cellular HIV infection in conjunction with the use of
 magnetic beads. . .

DETD . . . The whole cell with the intact surface membrane protein marker
 unique to the cancer is exposed to one or more ***monoclonal***
 antibodies specific for the suspect tumor, or to a multiplex battery of
 many ***monoclonal*** antibodies with ranging specificities to
 detect the existence of neoplastic cells without regard to the specific
 tumor type. The confirmatory. . .

DETD [0285] Detection of Aberrant ***Prion*** Protein

DETD [0286] The sensitivity of detection of aberrant ***prion*** protein
 can be increased by, one, improving isolation of all ***prion***
 molecules normal and aberrant from a large specimen (plasma or other),
 and two, developing an assay process that will permit a single
 pathologic ***prion*** to produce an amplified signal that will
 support its detection.

DETD [0288] STM/ ***Prion*** Sorting in Soluble Protein Samples

DETD [0289] One embodiment of ***prion*** sorting in a protein sample can
 be achieved by attachment of a ***monoclonal*** antibody specific
 for the C-terminal end of the molecule to a magnetic bead. The magnetic
 beads are placed in a . . . or brain biopsy extract or any other and
 mixed. The epitopes available for interaction on the C-terminal end of
 the ***prion*** molecule remain exposed in both the normal and
 aberrant ***prion*** molecule.

DETD [0290] The magnetic beads are collected with a magnet and washed in
 buffer. All the ***prion*** present in the sample will be separated
 from all other soluble proteins. The C-terminal antibody will capture
 the normal and pathologic ***prions*** due to the continued
 accessibility of the epitopes of both forms even after the transition
 has occurred.

DETD [0291] In this embodiment the ***prion*** sorted magnetic bead is
 treated with a ***monoclonal*** antibody available to the N-terminal
 end of the ***prion*** molecule (the .beta. sheet isoform end) that
 is labeled with an alkaline phosphatase polymer or any label known to
 those. . .

DETD [0292] The N-terminal end of the pathologic ***prion*** has
 undergone a transition from an .alpha. to a .beta. sheet form. During
 this transition, epitopes, normally found on the. . .

DETD [0293] ***Monoclonal*** antibodies specific for the N-terminal end
 of the pathologic ***prion*** are necessary for use in these
 sensitive diagnostic assay embodiments.

DETD . . . would be able to detect 0.01 attomoles quantities of alkaline
 phosphatase enzyme. Theoretically, supporting increased sensitivity than
 that achieved by ***prion*** precipitation by sodium
 phosphotungstate and time resolved fluorescence previously mentioned.

DETD [0295] STM MACMSA Sensitive Detection of Pathologic ***Prions***

DETD [0296] Another embodiment of STM for pathologic ***prion*** detection calls for use of sensitized RBC stroma to remove the pathologic ***prion*** (not the normal ***prion***) from a large sample. This can be achieved by attachment, as herein described, of a ***monoclonal*** antibody specific to the N-terminal end (sheet isoform) of the pathologic ***prion*** , which will not interact with the normal ***prion*** .

DETD . . . fresh complement, resulting in production of C3a ICPs directly proportional in number to the number of the .beta. sheet isoform ***prion*** molecules present.

DETD [0298] Theoretically each pathologic ***prion*** in this embodiment will generate a minimum of 40,000 C3a peptides for analysis.

DETD [0300] Although automation of this embodiment is difficult, some possibilities involve the usage of magnetic beads coated, not only with ***monoclonal*** antibody to the .beta. sheet isoform N-terminal end, but also coated with a lipid matrix to exploit the full amplification.

DETD [0301] The theoretical enhanced sensitivity of this detection methodology and MACMSA signal amplification should exceed that achieved by ***prion*** precipitation by sodium phosphotungstate and time resolved fluorescence previously discussed.

DETD . . . would still provide an acceptably lower sensitivity screening method would be to mix the solution containing the .beta. sheet pathologic ***prion*** isoform with immunoerythrocytes sensitized with an antibody specific to an exposed epitope on the N-terminal end of the pathologic ***prion*** . A large sample may be used. This mix is followed by the addition of fresh complement. Theoretically, a single pathologic ***prion*** could cause the lysis of a single sensitized RBC. A positive assay result would be detected as lysis of the . . .

DETD [0329] 20. Safar, J, Wille, H, Itri, V, et al. Eight ***prion*** strains have PrPsc molecules with different conformations. Nature Medicine October 1998 Vol.4 (10):1157-1165

L12 ANSWER 19 OF 23 USPATFULL on STN

AN 2002:242778 USPATFULL

TI Method for purifying a biological composition

IN Chapman, John, Newton, MA, UNITED STATES

Purmal, Andrei, Waltham, MA, UNITED STATES

Hope, James, Newtonville, MA, UNITED STATES

PI US 2002131958 A1 20020919

AI US 2001-945979 A1 20010904 (9)

RLI Continuation-in-part of Ser. No. US 2001-827491, filed on 6 Apr 2001, PENDING

PRAI US 2001-263417P 20010122 (60)

DT Utility

FS APPLICATION

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CLMN Number of Claims: 61

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1797

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method for reducing the amount of extracellular fluid in a blood cell suspension. The method includes providing a large volume of a blood cell suspension that includes blood cells and extracellular fluid. The blood cell suspension is washed with a wash solution under conditions sufficient to lower the concentration of the extracellular fluid in the blood cell composition at least 10.sup.3-fold relative to the amount of extracellular fluid in the blood cell suspension. The method can also be used to lower the concentration of analytes (such as

prions) in the blood cell suspension. Also provided is a blood cell suspension produced by the washing method.

AB . . . fluid in the blood cell suspension. The method can also be used to lower the concentration of analytes (such as ***prions***) in the blood cell suspension. Also provided is a blood cell suspension produced by the washing method.

SUMM [0002] The invention relates to methods for removing analytes, such as ***prion*** proteins, from biological fluids, such as blood.

SUMM . . . of an undesired macromolecule in a donor blood cell suspension which may be potentially harmful to a recipient such as: ***prion*** proteins which can cause neurologic disorders; enzymes, antibodies and cytokines that can produce inflammatory and febrile reactions in a recipient;. . . Examples of protein analytes whose levels in blood cell suspension are reduced according to the methods of the inventions are ***prion*** proteins, cytokines (e.g., interleukin 1 beta, tumor necrosis factor alpha, interleukin 6, interleukin 8, interleukin 10), inflammatory enzymes (neutrophil elastase,. . .

SUMM . . . Examples of protein analytes whose levels in blood cell suspension are reduced according to the methods of the inventions are ***prion*** proteins, particularly pathogenic ***prion*** protein. Other examples of analytes that are removed by the methods of the invention can include, cells, e.g. leukocytes, microbial. . .

SUMM [0029] In a preferred embodiment where the analyte to be reduced in a blood cell suspension is a ***prion*** protein, the amount of ***prion*** protein is reduced at least 10 fold, preferably 10.sup.2-fold relative to the amount of the ***prion*** protein in the starting blood cell suspension by the methods of the invention. Preferably, ***prion*** protein (PrP) is reduced at least 10.sup.3-fold, 10.sup.4-fold or 10.sup.5-fold relative to the amount of the ***prion*** protein in the first blood cell suspension. More preferably, washing is sufficient reduce the amount of the ***prion*** protein at least 10.sup.6-fold, 10.sup.7-fold or 10.sup.8-fold relative to the amount of the ***prion*** protein in the starting blood cell suspension. More preferably, the ***prion*** protein is reduced at least 10.sup.9-fold or 10.sup.10-fold relative to the amount of ***prion*** protein in the starting blood cell suspension.

SUMM [0030] In one embodiment of the invention, ***prion*** protein, is reduced in a blood cell suspension by the washing procedures of the invention. In another embodiment, ***prion*** protein is reduced in a blood cell suspension by the washing procedures of the invention wherein the wash solution comprises a lipophilic emulsion. In another embodiment of the invention, ***prion*** protein is reduced in a blood cell suspension by the washing procedures of the invention in combination with running the blood cell suspension through a blood compatible filter, preferably a leukoreducing filter. In another preferred embodiment, ***prion*** protein is reduced in a blood cell suspension by the wash procedures of the invention wherein the wash solution comprises. . .

SUMM [0031] In a preferred embodiment, the ***prion*** protein removed and/or reduced by the above methods of the invention is a pathogenic ***prion*** protein. In particularly preferred embodiments the ***prion*** protein removed and/or reduced by the above methods of the invention is an endogenous blood borne ***prion*** protein. In particularly preferred embodiments, the ***prion*** protein removed and/or reduced by the methods of the invention is a pathogenic blood-borne ***prion*** protein. In a particularly preferred embodiment, the pathogenic blood-borne ***prion*** protein is removed from a mammalian red blood suspension, particularly from mammalian (e.g. human) whole blood or red cell concentrate.

SUMM [0032] In a preferred embodiment, where the ***prion*** protein to be reduced and/or removed in a blood cell suspension comprises soluble

prion protein, the soluble ***prion*** protein may be reduced by the washing procedures of the invention. In a preferred embodiment where the ***prion*** protein to be reduced and/or removed in a blood cell suspension comprises a membrane-associate ***prion*** protein, a lipophilic emulsion may be added to the washing buffer of the invention and/or the blood cell suspension may be run through a blood compatible filter. In preferred embodiments where the ***prion*** protein is reduced and/or removed from the blood cell suspension comprises an insoluble ***prion*** protein, a lipophilic emulsion may be added to the washing buffer of the invention and/or the blood cell suspension may be run through a blood compatible filter. In preferred embodiments where the ***prion*** protein to be reduced and/or removed from the blood cell suspension comprises multiple physical forms of ***prion*** protein a combination of washing, filtration and/or lipophilic emulsion can be used to achieve the above described log reductions.

SUMM [0033] In preferred embodiments, the blood cell suspension is assayed for the presence or absence of ***prion*** protein prior to and/or following washing procedures or wash/filter combinations of the invention. In particularly preferred embodiments, a red blood cell suspension is assayed for the presence or absence of pathogenic ***prion*** protein and/or aggregates following the washing or wash filter combinations of the invention. Detection of residual ***prion*** protein can follow an optional concentration step for concentrating ***prion*** protein, if any, remaining associated with the red blood cell composition following the wash procedures or wash/filter combinations of the . . .

SUMM [0034] In a particularly preferred embodiment, transmission or the risk of a ***prion*** mediated disease, particularly a transmissible spongiform encephalopathy, by a blood product is reduced. In another particularly preferred embodiment, the onset of a ***prion*** mediated disease, particularly a transmissible spongiform encephalopathy, is significantly delayed from the time of potential exposure via a blood product. In a preferred embodiment, reduction of the risk of transmission or delay in the onset of a ***prion*** mediated disease, particularly a transmissible spongiform encephalopathy, is provided by the following methods of the invention. Washing or washing and. . . filtering a blood cell suspension according to the methods of the invention, thereby reducing the concentration of extracellular protein, preferably ***prion*** protein, particularly pathogenic ***prion*** protein. Transfusing the washed blood cell suspension to a recipient. In a particularly preferred embodiment, the recipient is a human. . .

SUMM . . . Detection in the reduction of extracellular protein may comprise detecting a reduction in the concentration of extracellular IgG, serum albumin, ***prion*** protein and/or pathogenic ***prion*** protein.

SUMM . . . that of a second washed blood cell unit where the second washed blood cell unit has been tested for infectious ***prion*** protein in a bioassay. In particularly preferred embodiments, the second washed blood cell unit results in a lower incidence of onset of a ***prion*** mediated disease, particularly a transmissible spongiform encephalopathy, in an animal bioassay compared to the incidence observed for an unwashed control. In another preferred embodiment the second washed blood cell unit results in a delayed onset of a ***prion*** mediated disease, particularly a transmissible spongiform encephalopathy in an animal bioassay compared to that observed in the bioassay for the . . . unwashed control. In particularly preferred embodiments the washed blood cell suspension to be transfused comprises an extracellular IgG, serum albumin, ***prion*** protein and/or pathogenic ***prion*** protein concentration correlated to that of a blood cell unit that does

not result in onset of a ***prion*** mediated disease, particularly a transmissible spongiform encephalopathy in a bioassay or results in delayed onset of a ***prion*** mediated disease, particularly a transmissible spongiform encephalopathy, in a bioassay.

SUMM [0044] A " ***prion*** mediated disease" as defined herein relates to a disease associated with the finding of ***abnormal***

prion protein and includes transmissible spongiform encephalopathy such as scrapie, bovine spongiform encephalopathy, Creutzfeldt-Jakob disease (CJD), and variant Creutzfeldt-Jakob disease.

SUMM . . . Examples of protein analytes whose levels in blood cell suspension are reduced according to the methods of the inventions are ***prion*** proteins, particularly pathogenic ***prion*** protein.

Other examples of analytes that are removed by the methods of the invention can include, cells, e.g. leukocytes, microbial. . .

SUMM [0049] The term ***prion*** is a synonym for the infectious agent which causes transmissible spongiform encephalopathies-for example, human variant CJD, cattle BSE, and scrapie. . . in sheep. The method of the invention can be used to remove and/or reduce the amount of any form of ***prion*** protein in biological compositions, particularly in blood cell suspensions. The term ***prion*** protein (PrP), as used herein includes the naturally-occurring, non-infectious forms (generically known as PrP.sup.C), the pathogenic forms (generically known as. . . .beta.-(.beta.-recPrP) secondary structure, or supra-molecular aggregates of one or a combination of these forms (aggregated PrP or PrP.sup.AG). The term ***prion*** protein as used herein includes any physical form of PrP, e.g. PrP characterized by being soluble, insoluble, protease-sensitive, protease-insensitive, membrane-associated,. . . as used herein is used in the broad sense of an infectious protein and/or a simple product of disease. Pathogenic ***prion*** proteins of the invention, therefore, include any of the foregoing proteins that are infectious and/or are products of disease.

SUMM [0050] ***Prion*** protein, including pathogenic ***prion*** protein, further including blood borne pathogenic ***prion*** protein may be detected in a variety of ways including using one or more of the following methods: using antibodies,. . . O., Tremblay, P., DeArmond, S. J., and Prusiner, S. B. (1999). Compelling transgenic evidence for transmission of bovine spongiform encephalopathy ***prions*** to humans. Proc Natl Acad Sci U S A 96, 15137-42. Moore, R. C. and Melton, D. W. (1997). Transgenic analysis of ***prion*** diseases. Mol Hum Reprod 3, 529-44. Race, R. E., Priola, S. A., Bessen, R. A., Ernst, D., Dockter, J., Rall, G. F., Mucke, L., Chesebro, B., and Oldstone, M. B. (1995). Neuron-specific expression of a hamster ***prion*** protein minigene in transgenic mice induces susceptibility to hamster scrapie agent. Neuron 15, 1183-91; Telling, G. C., Scott, M., Hsiao, . . . DeArmond, S. J., and Prusiner, S. B. (1994). Transmission of Creutzfeldt-Jakob disease from humans to transgenic mice expressing chimeric human-mouse ***prion*** protein. Proc Natl Acad Sci U S A 91, 9936-40.; 7. Westaway, D., Mirenda, C. A., Foster, D., Zebardjian, Y., . . . L., Serban, H., DeArmond, S. J., Ebeling, C., et al (1991). Paradoxical shortening of scrapie incubation times by expression of ***prion*** protein transgenes derived from long incubation period mice. Neuron 7, 59-68.; Prusiner, S. B., Scott, M., Foster, D., Pan, K., . . . S. L., Serban, D., Carlson, G. A., et al (1990). Transgenic studies implicate interactions between homologous PrP isoforms in scrapie ***prion*** replication. Cell 63, 673-86.), using a cell based bioassay, see, e.g Birkett, C. R., Hennion, R. M., Bembridge, D. A., . . . Lehmann, S., and Laude, H. (2001). Ex vivo propagation of infectious sheep scrapie agent in heterologous epithelial cells expressing ovine ***prion*** protein. Proc Natl Acad Sci U S A 98,4055-9); and according to the examples described herein.

SUMM [0051] Onset of ***prion*** mediated disease, including

transmissible spongiform encephalopathy, in animal bioassays may be detected by observing the animals for clinical signs of. . . Immunohistochemical and Western blot screening of several discrete brain sections and sections of peripheral lymphoid tissues for the presence of ***abnormal*** ***prion*** protein are recommended to confirm TSE disease.

SUMM . . . contaminated blood cell preparations can range in size from high order fibrillar aggregates to an abnormally folded monomeric protein. Accordingly, ***prions*** can be i) present in the surrounding fluid, ii) non-covalently attached to the erythrocyte surface by ionic or hydrophobic interactions, or iii) partially integrated into the RBCC membrane via its GPI membrane anchor. Therefore, it is postulated that ***prion*** reduction can be achieved according to the invention by exhaustive washing where continuous reduction of ambient PrP^{sup.Sc} shifts association equilibria. . .

SUMM . . . the wash solution of invention, particularly where the analyte to be removed and/or reduced in blood cell suspension is a ***prion*** protein or a lipid enveloped virus. Such a lipophilic emulsion can be composed of the same composition as those used. . .

DETD . . . for 1 hour at room temperature (alternatively overnight at 4 degrees). The blot is incubated with human serum albumin-specific human ***monoclonal*** antibody (clone # HAS-11, Sigma, lot # 129H4847). Antibody is diluted in 1.times. PBS solution at 1:2000 dilution and placed. . .

DETD . . . temperature (alternatively overnight at 4 degrees). For analysis of HSA, the blot is incubated with human serum albumin (HSA)-specific human ***monoclonal*** antibody (clone # HSA-I 1, Sigma, A8763). Antibody is diluted in IX blocking solution at 1:2000 dilution and placed in. . .

DETD Preparation of ***Prion*** Protein Spiking Material

DETD [0126] D. Normal ***Prion*** Protein from Human Platelets (huPltPrP^{sup.C})

DETD [0132] The recombinant .alpha. and .beta. forms of full-length ***prion*** protein are obtained from the TSE Resource Centre, Institute for Animal Health, Compton, Berkshire, UK. Essentially the protein is expressed. . . CuCl₂.sub.2 dialysis method of Jackson and colleagues (Jackson, G. S., et al. (1999). Multiple folding pathways for heterologously expressed human ***prion*** protein. Biochim Biophys Acta 1431, 1-13). Recombinant PrP .beta.-form was made from rPrP .alpha.-form. (Jackson G. S., et al. 1999).. . .

DETD Removal of ***Prion*** Protein by Automated Wash Procedure

DETD Removal of ***Prion*** Protein by Manual Wash Procedure

DETD . . . of extracellular protein via the procedure of Example 1A or 1B, e.g. reduction of IgG and/or serum albumin and/or cellular ***prion*** protein and/or infectious ***prion*** protein is monitored as described in any of the Examples 5, 7, or 9 above.

DETD . . . Chong, A., Bruce, M. E., Cairns, D., Goldmann, W., Hunter, N., and Bostock, C. J. (1999). Molecular analysis of ovine ***prion*** protein identifies similarities between BSE and an experimental isolate of natural scrapie, CH1641. J Gen Virol 80 (Pt 1), 1-4). . .

DETD . . . RBCC unit and unwashed control is assessed for the concentration of extracellular protein, such as IgG or serum albumin, cellular ***prion*** protein and/or pathogenic ***prion*** protein as described in Example 5, 7 or 9 above. The recipient mice can be susceptible transgenic lines such as. . .

DETD . . . 1A or 1B above. The human RBCC is assayed for concentration of extracellular protein, such as IgG or serum albumin, ***prion*** protein and/or pathogenic ***prion*** protein as described in Example 5, 7 or 9 above. RBCC comprising an extracellular protein concentration that correlates to that. . .

CLM What is claimed is:

14. The method of claim 13, wherein the protein is a ***prion*** protein.
15. The method of claim 14, wherein the ***prion*** protein is a pathogenic ***prion*** protein.
16. The method of claim 15, further comprising detecting a reduction of pathogenic ***prion*** protein.
18. The method of claim 12, further comprising detecting a reduction of pathogenic ***prion*** protein.
20. The method of claim 19, further comprising detecting the reduction of pathogenic ***prion*** protein.
22. The method of claim 21, further comprising detecting a reduction of pathogenic ***prion*** protein.
27. The method of claim 26, comprising detecting a reduction of a ***prion*** protein.
28. The method of claim 27, comprising detecting a reduction of a pathogenic ***prion*** protein.
32. A method for lowering the concentration of an pathogenic ***prion*** protein in a blood cell composition, the method comprising: (i) providing a mammalian blood cell suspension comprising red blood cells. . . (ii) washing the blood cell suspension with a wash solution under conditions sufficient to lower the concentration of the pathogenic ***prion*** protein relative to the concentration of the pathogenic ***prion*** protein in the first mammalian blood cell suspension.
33. The method of claim 32, further comprising assaying the blood cell suspension for the presence or absence of pathogenic ***prion*** protein.
34. The method of claim 33, further comprising detecting at least a one log reduction of pathogenic ***prion*** protein concentration relative to the pathogenic ***prion*** concentration of the first mammalian blood cell suspension.
35. The method of claim 32, further comprising assaying the blood cell composition for the presence or absence of ***prion*** protein.
36. The method of claim 35 further comprising detecting about at least a 100 log reduction of ***prion*** protein
45. The method of claim 44, wherein the reduced extracellular protein is a ***prion*** protein.
46. The method of claim 45, wherein in the reduced ***prion*** protein is a pathogenic ***prion*** protein.
47. The method of claim 47 wherein the extracellular protein is selected from the group consisting of serum albumin, IgG, a cytokine and ***prion*** protein.
49. The method of claim 48, wherein the extracellular protein is a pathogenic ***prion*** protein.

L12 ANSWER 20 OF 23 USPATFULL on STN

AN 2002:78467 USPATFULL

TI Mammalian proteins; related reagents and methods

IN Bazan, J. Fernando, Palo Alto, CA, UNITED STATES

PI US 2002042122 A1 20020411

AI US 2000-745003 A1 20001220 (9)

PRAI US 1999-172090P 19991223 (60)

DT Utility

FS APPLICATION

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CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2359

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Mammalian polypeptides, isolated proteins, and fragments thereof including the polynucleotides encoding them. Antibodies, both polyclonal and ***monoclonal***, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are provided.

AB Mammalian polypeptides, isolated proteins, and fragments thereof including the polynucleotides encoding them. Antibodies, both polyclonal and ***monoclonal***, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are provided.

SUMM [0003] ***Prions*** are proteinaceous compositions suspected of acting as infectious pathogens in mammalian central nervous system disease. A major advance in the study of neurodegenerative disease was the discovery and purification of a protein designated ***prion*** protein (PrP). Bolton, et al. (1982) Science 218:1309-11; Prusiner, et al. (1982) Biochemistry 21:6942-50; and McKinley, et al. (1983) Cell. .

SUMM . . . the human diseases: Kuru, Creutzfeldt-Jakob Disease (CJD), Gerstmann-Straussler-Scheinker Disease (GSS), and fatal familial insomnia (FFI) are all suspected of being ***prion*** -associated diseases caused by insoluble PrP.sup.Sc isoforms. Gajdusek (1977) Science 197:943-960; and Medori, et al. (1992) N. Engl. J. Med. 326:444-449.

SUMM [0006] Accordingly, there exists a need for the discovery and development of additional ***prion*** -like compositions similar to PrPs. Such a discovery will further our understanding of ***prion*** -like compositions in normal and disease states and permit development of new therapies to ameliorate associated abnormal conditions. The present provides new mammalian ***prion*** -like compositions designated PrP2s, related compositions, e.g., genes and antibodies, and methods for their research, diagnostic, or therapeutic use.

SUMM [0035] B. ***monoclonal***

SUMM [0050] The present invention provides amino acid and DNA sequences of mammalian, particularly primate and rodent ***prion*** -like molecules, designated PrP2, having particular defined properties, both structural and biological. These embodiments increase the number of members of the human ***prion*** -like (PrP) family from one to two, but also serve to establish that the family consists of more than a single. . .

SUMM [0053]

TABLE 2

Alignment of PrP2s (SEQ ID NO: 2 and 4) with ***prion*** (PrPs) specie variants (e.g., Bovine PrP SEQ ID NO: 9; Chick PrP

SEQ ID NO: 8; Human PrP SEQ ID NO: . . .

SUMM . . . to cell in such a manner. Methods of inhibiting such transfers are encompassed herein as a means to prevent PrP2 ***prion*** -like disease transmission. One technique is cleaving and/or releasing PrP2 from its GPI anchor to release it from its associated cell. . .

SUMM . . . and metabolic variants of the mammalian protein. For example, it has been shown that specific molecular features characterize the protease-resistant ***prion*** protein (PrP) detected in animal species as well as in humans infected by the infectious agent strain that causes bovine. . .

SUMM . . . Johnson (1976) Protein Crystallography, Academic Press, New York (incorporated herein by reference). Additional methods of detecting other moieties that bind ***prion*** -like compositions are described, e.g., in U.S. Pat. No. 5,679,530. Such techniques can also be applied to PrP2s of the present. . .

SUMM [0070] The PrP2s will exhibit immunogenic activity, e.g., elicit a selective immune response. Particular techniques to generate antibodies to ***prion*** -like compositions can be used with PrP2s of the instant invention. These methods described in U.S. Pat. No. 5,846,533, (incorporated by. . .

SUMM . . . segment provided in SEQ ID NO: 1, 3, 5, or 13 but preferably not with a corresponding segment of other ***prion*** -like compositions. The protein or polypeptide can be a full-length protein or fragment that will typically have a polypeptide segment highly. . .

SUMM . . . genetic code, encode polypeptides equivalent to fragments of PrP2 and fusions of sequences from various different related molecules, e.g., other ***prion*** -like members.

SUMM . . . polypeptide segments that are not normally fused in the same manner. Thus, a fusion product of a PrP2 with another ***prion*** or ***prion*** -like composition encompasses a continuous polypeptide having sequences fused in a typical peptide linkage, typically made as a single translation product. . .

SUMM [0092] The present invention also particularly provides PrP2 muteins that are ***prion*** -like compositions. Structural alignment of PrP2s with related ***prion*** family members illustrate conserved features/residues. See, e.g., Tables 1 and 2.

SUMM [0093] Similar variations in other species counterparts of ***prion*** -like sequences, should provide similar interactions with a ligand or substrate. Substitutions with either rodent or primate sequences, e.g., mouse or. . .

SUMM . . . Fusion polypeptides between PrP2s and other homologous or heterologous proteins are also provided. Homologous polypeptides encompass any fusions between different ***prion*** -like compositions, resulting in, e.g., a hybrid protein with binding specificity for multiple different PrP2s. Likewise, heterologous fusions exhibiting a combination. . .

SUMM . . . as an immunogen to produce specific antisera or antibodies, e.g., that distinguish PrP2s, portions thereof, various PrP2 conformations, or other ***prion*** family members (PrPs). A purified PrP2 can be used to screen ***monoclonal*** antibodies or antigen-binding fragments prepared by immunization with various forms of impure preparations containing PrP2 protein or polypeptide. The term. . .

SUMM . . . variety of host cells to synthesize full-length PrP2 or fragments that can be used, for example, to generate polyclonal or ***monoclonal*** antibodies; for binding studies; for construction and expression of modified ligand binding or kinase/phosphatase domains; and for structure/function studies. Variants. . .

SUMM . . . fragments and single chain versions, can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. ***Monoclonal*** antibodies are prepared from

cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective protein, or screened for agonistic or antagonistic activity. These ***monoclonal*** antibodies will usually bind with at least a $K_{sub.D}$ of about 1 mM, more usually at least about 300 .mu.M. . .

SUMM . . . can be potent antagonists by binding and inhibiting other compositions from binding; or they can inhibit the ability of a ***prion*** -like composition to elicit a biological response, e.g., act on its substrate. They can also be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides to bind producing cells, or cells localized to the source of the ***prion***. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a . . .

SUMM [0132] In some instances, it is desirable to prepare ***monoclonal*** antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such ***monoclonal*** antibodies can be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, Calif., and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) ***Monoclonal*** Antibodies: Principles and Practice (2d ed.) Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256:495-497, discussing a method of generating ***monoclonal*** antibodies. Summarized briefly, an animal is injected with an immunogen, sacrificed, then spleen cells are removed and fused with myeloma. . .

SUMM . . . a protein, e.g., of SEQ ID NO: 2, 4, or 6. Such antiserum is selected for low crossreactivity to other ***prion*** family members, e.g., PrPs, preferably from the same species, and any crossreactivity is removed by immunoabsorption before use of the. . .

SUMM . . . solid support. Polyclonal antisera with a titer of 10.sup.4 or greater are selected and tested for cross reactivity to other ***prion*** family members using a competitive binding immunoassay (such as described supra, Harlow and Lane pp. 570-573). Preferably, at least two PrP2s or PrP family members are used in this determination. These ***prion*** family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques.

SUMM . . . antigen. The ability of the proteins to compete with the antisera to bind an immobilized antigen is compared to other ***prions***, e.g., PrP2 or PrPs. A degree of crossreactivity is then calculated. Antisera with less than 10% crossreactivity to each test. .

SUMM . . . sequences of a PrP2. These sequences can be used as probes to detect PrP2 in patients suspected of having a ***prion*** disorder. Preparation of both RNA and DNA nucleotide sequences, labeling of the sequences, and determining their preferred size of the. . .

SUMM . . . with compounds identified as having binding affinity to the PrP2s or antibodies. These reagents are useful in ameliorating conditions of ***abnormal*** ***prion*** expression. Some ***prion*** -like conditions require participation of immune system cells. See, Scrapie replication in lymphoid tissues depends on ***prion*** protein-expressing follicular dendritic cells by Brown, et al. (1999) Nature Medicine 5: 1308-12. Additionally, the invention provides therapeutic value for various conditions or states associated with abnormal expression or abnormal triggering of response to a ***prion***, or ***prion*** -like composition. See, e.g., Prusiner (1991) Science 252:1515-1522; Wilesmith and Wells (1991) Microbiol. Immunol. 172:21-38; Gajdusek (1977) Science 197:943-960; and Medori,. .

SUMM . . . of this invention may be combined or used in with other

therapeutic agents, e.g., with agonists or antagonists of other
prion-like compositions.

DETD [0168] Many techniques applicable to other ***prion*** compositions
(e.g., PrPs) as described, e.g., in U.S. Pat. Nos.: 5,891,641,
5,834,593, 5,846,533, 5,792,901, 5,679,530, and 5,908,969 (all of which.

DETD [0170] Human PrP2 sequences related to published ***prion***
sequences (PrPs) were identified from various EST databases using, e.g.,
the BLAST server. Altschul, et al. (1994) Nature Genet. 6:119-129..

DETD [0171] III. Cloning of full-length human ***prion*** cDNAs.

DETD . . . and induced with IPTG (Sigma, St. Louis, Mo.). After overnight
induction, the bacteria are harvested and the pellets containing the
prion8 protein are isolated. The pellets are homogenized, e.g.,
in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and. . .

DETD [0189] ***Monoclonal*** antibodies may be made. For example,
splenocytes are fused with an appropriate fusion partner and hybridomas
are selected in growth. . .

DETD [0190] In another method, synthetic peptides or purified PrP2 is
presented to an immune system to generate ***monoclonal*** or
polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in
Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A
Laboratory. . .

DETD . . . antibodies binding PrP proteins, e.g., disease forms of PrP.
The difficulty relates, in part, to special qualities of the
disease-related ***prion*** conformation. However, by following
procedures described in U.S. Pat. Nos.: 5,846,533 and 5,792,901
(incorporated herein in their entirety) for generating. . .

DETD [0192] When considering presenting an antigen to a mouse with the goal
of obtaining specific ***monoclonal*** antibodies against a
misfolded or aggregated form of a host protein, it is desirable to
increase the definition of a . . . that a particular population of
protein conformation passes an antigenic threshold necessary to start an
immunogenic response. Pulling out the ***monoclonal*** antibodies by
correct screening is essential. Screening against the pure misfolded or
aggregated protein is often complicated by its poor. . .

DETD [0193] Another technique for creating ***monoclonal*** antibodies
specific for the native, disease-associated isoform of the PrP
prion is taught by Korth et al. (1999) Methods Enzymol.
309:106-122 and can be adapted here for use with PrP2 without requiring
undue experimentation. Korth, et al., review the circumstances leading
to the first ***monoclonal*** antibody against the
disease-associated form of PrP. Using this analysis, Korth, et al.,
teach a reliable conformational screening protocol for. . .

DETD . . . The method is based on nucleic acid injection into non tolerant
PrP^{-/-} mice. DNA or RNA coding for different human ***prion***
proteins including the mutated sequences associated with CJD, GSS, and
FFI is injected into muscle tissue. Initially, the mice are. . . The
resulting mAbs are directed against four different linear epitopes of
PrP and may recognize discontinuous regions of the native ***prion***
protein. Immunization of non tolerant mice with DNA and live attenuated
SF virus can induce a broad immune response eventually. . .

DETD . . . hybrid system construct. See, e.g., Fields and Song (1989)
Nature 340:245-246. Alternatively, the technique of Scott, et al. (1992)
Chimeric ***prion*** protein expression-in cultured cells and
transgenic mice Protein Sci. 1:986-997 can be adopted for use with PrP2.

DETD . . . enzyme, or other standard label. Detecting presence of PrP2 in
a sample may indicate presence of, or predisposition toward, a
prion-type associated disorder, such as those described herein
or in the art.

DETD . . . to identify PrP2 in samples, thus providing a method of

screening and/or diagnosis, especially when other symptoms characteristic of a ***prion*** associated disorder are observed. In view of the prevalence of ***prion*** associated disorders in livestock, e.g., there are both human and veterinary uses for the PrP2s of this invention.

L12 ANSWER 21 OF 23 USPATFULL on STN

AN 1999:63442 USPATFULL

TI Method of detecting ***prions*** in a sample and transgenic animal used for same

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RLI Continuation-in-part of Ser. No. US 1995-509261, filed on 31 Jul 1995, now patented, Pat. No. US 5763740 which is a continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994, now patented, Pat. No. US 5565186

DT Utility

FS Granted

EXNAM Primary Examiner: Stanton, Brian R.; Assistant Examiner: Beckerleg, Anne Marie S.

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CLMN Number of Claims: 7

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 2687

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention includes an artificial PrP gene, a transgenic animal containing a PrP gene of another animal or the artificial PrP gene, a hybrid non-human mammal with an ablated endogenous ***prion*** protein gene and exogenous ***prion*** protein gene, assay methodology which uses the animals to detect pathogenic ***prions*** in a sample or diagnose a cause of death and standardized ***prion*** preparation used in the assay. The genome of a host animal (such as a mouse), is manipulated so that the animal is rendered susceptible to infection with ***prions*** which normally would infect only a genetically diverse test animal (such as human, cow or sheep). Pathogenic ***prions*** in a sample can be detected by injecting the sample to be tested into a mammal of the invention which has been genetically manipulated so as to be susceptible to infection from ***prions*** in the sample. Mammals which are not inoculated with the sample and others inoculated with a standardized ***prion*** preparation of the invention are used as controls in the assay to detect ***prions*** in samples which cause diseases. For example, Creutzfeldt Jakob Disease (CJD) is a fatal neurodegenerative disease of humans caused by ***prions***. The mammals disclosed herein develop the adverse effects of such ***prions*** in a relatively short time after being inoculated with human ***prions***.

TI Method of detecting ***prions*** in a sample and transgenic animal used for same

AB . . . containing a PrP gene of another animal or the artificial PrP gene, a hybrid non-human mammal with an ablated endogenous ***prion*** protein gene and exogenous ***prion*** protein gene, assay methodology which uses the animals to detect pathogenic ***prions*** in a sample or diagnose a cause of death and standardized ***prion*** preparation used in the assay. The genome of a host animal (such as a mouse), is manipulated so that the animal is rendered susceptible to

infection with ***prions*** which normally would infect only a genetically diverse test animal (such as human, cow or sheep). Pathogenic ***prions*** in a sample can be detected by injecting the sample to be tested into a mammal of the invention which has been genetically manipulated so as to be susceptible to infection from ***prions*** in the sample. Mammals which are not inoculated with the sample and others inoculated with a standardized ***prion*** preparation of the invention are used as controls in the assay to detect ***prions*** in samples which cause diseases. For example, Creutzfeldt Jakob Disease (CJD) is a fatal neurodegenerative disease of humans caused by ***prions***. The mammals disclosed herein develop the adverse effects of such ***prions*** in a relatively short time after being inoculated with human ***prions***.

SUMM . . . animals used in such assays. More specifically, this invention relates to artificial and chimeric PrP genes, assaying samples for pathogenic ***prions***, standardized ***prion*** preparations used in such assays and to transgenic mice and hybrid transgenic mice which can be infected with ***prions*** which generally only infect a genetically diverse species.

SUMM ***Prions*** are infectious pathogens that cause central nervous system spongiform encephalopathies in humans and animals. ***Prions*** are distinct from bacteria, viruses and viroids. The predominant hypothesis at present is that no nucleic acid component is necessary for infectivity of ***prion*** protein. Further, a ***prion*** which infects one species of animal (e.g., a human) will not infect another (e.g., a mouse).

SUMM A major step in the study of ***prions*** and the diseases that they cause was the discovery and purification of a protein designated ***prion*** protein ("PrP") [Bolton et al., Science 218:1309-11 (1982); Prusiner et al., Biochemistry 21:6942-50 (1982); McKinley et al., Cell 35:57-62 (1983)]. Complete ***prion*** protein-encoding genes have since been cloned, sequenced and expressed in transgenic animals. PrP.sup.C is encoded by a single-copy host gene. . . et al., Cell 46:417-28 (1986)] and is normally found at the outer surface of neurons. A leading hypothesis is that ***prion*** diseases result from conversion of PrP.sup.C into a modified form called PrP.sup.Sc. However, the actual biological or physiological function of . . .

SUMM It appears that the scrapie isoform of the ***prion*** protein (PrP.sup.Sc) is necessary for both the transmission and pathogenesis of the transmissible neurodegenerative diseases of animals and humans. See Prusiner, S. B., "Molecular biology of ***prion*** disease," Science 252:1515-1522 (1991). The most common ***prion*** diseases of animals are scrapie of sheep and goats and bovine spongiform encephalopathy (BSE) of cattle [Wilesmith, J. and Wells, Microbiol. Immunol. 172:21-38 (1991)]. Four ***prion*** diseases of humans have been identified: (1) kuru, (2) Creutzfeldt-Jakob Disease (CJD), (3) Gerstmann-Strassler-Scheinker Disease (GSS), and (4) fatal familial . . . (FFI) [Gajdusek, D. C., Science 197:943-960 (1977); Medori et al., N. Engl. J. Med. 326:444-449 (1992)]. The presentation of human ***prion*** diseases as sporadic, genetic and infectious illnesses initially posed a conundrum which has been explained by the cellular genetic origin. . .

SUMM . . . While the most reliable transmission data has been said to emanate from studies using non-human primates, some cases of human ***prion*** disease have been transmitted to rodents but apparently with less regularity [Gibbs, Jr. et al., Slow Transmissible Diseases of the . . . Vol. 2, S. B. Prusiner and W. J. Hadlow, eds. (New York: Academic Press), pp. 87-110 (1979); Tateishi et al., ***Prion*** Diseases of Humans and Animals, Prusiner et al., eds. (London: Ellis Horwood), pp. 129-134 (1992)].

SUMM The infrequent transmission of human ***prion*** disease to rodents

has been cited as an example of the "species barrier" first described by Pattison in his studies. . . and M. P. Alpers, eds. (Washington, D.C.: U.S. Government Printing), pp. 249-257 (1965)]. In those investigations, the initial passage of ***prions*** from one species to another was associated with a prolonged incubation time with only a few animals developing illness. Subsequent. . .

SUMM . . . al., Proc. Natl. Acad. Sci. USA 83:6372-6376 (1986)]. Tg(SH_{PrP}) mice expressing SH_{PrP} had abbreviated incubation times when inoculated with SH_{PrP} ***prions***. When similar studies were performed with mice expressing the human, or ovine PrP transgenes, the species barrier was not abrogated, . . . and the incubation times were unacceptably long. Thus, it has not been possible, for example in the case of human ***prions***, to use transgenic animals (such as mice containing a PrP gene of another species) to reliably test a sample to determine if that sample is infected with ***prions***. The seriousness of the health risk resulting from the lack of such a test is exemplified below.

SUMM . . . used, although the seemingly remote possibility has been raised that increased expression of wtPrP^{sup.C} stimulated by high HGH might induce ***prion*** disease [Lasmezas et al., Biochem. Biophys. Res. Commun. 196:1163-1169 (1993)]. That the HGH prepared from pituitaries was contaminated with ***prions*** is supported by the transmission of ***prion*** disease to a monkey 66 months after inoculation with a suspect lot of HGH [Gibbs, Jr. et al., N. Engl. J. Med. 328:358-359 (1993)]. The long incubation times associated with ***prion*** diseases will not reveal the full extent of iatrogenic CJD for decades in thousands of people treated with HGH worldwide.. . . Lancet 340:24-27 (1992)]. These cases of iatrogenic CJD underscore the need for screening pharmaceuticals that might possibly be contaminated with ***prions***.

SUMM . . . of such, there clearly is a need for a convenient, cost-effective assay for testing sample materials for the presence of ***prions*** which cause CJD. The present invention offers such an assay.

SUMM . . . are the offspring of different transgenic animals with each other or with a transgenic animal that has an ablated endogenous ***prion*** protein gene, a standardized ***prion*** preparation and assay methodology which uses the preparation and genetically altered animals to detect pathogenic ***prions*** in a sample. The artificial gene includes a sequence such that when it is inserted into the genome of an animal (such as a mouse), the animal is rendered susceptible to infection with ***prions*** which normally would infect only a specific species of genetically diverse animal (such as a human, cow, sheep, pig, chicken,. . . resulting from a cross between two transgenic animals and in particular a cross between a transgenic animal containing the entire ***prion*** protein gene of a genetically diverse animal (e.g., a mouse containing a human ***prion*** protein gene) and an animal with its endogenous ***prion*** protein gene disrupted (e.g., a mouse with an ablated ***prion*** protein gene). Hybrids also specifically include crossing a transgenic animal having a chimeric ***prion*** protein gene with an animal with its endogenous ***prion*** protein gene ablated.

SUMM . . . the invention are used to create animals which due to their genetic make up will develop disease from inoculation with ***prions*** which would generally only infect a genetically diverse animal, e.g., a mouse of the invention will consistently become infected with ***prions*** which generally will only infect a human and symptoms of the infection will become apparent in a short period e.g., . . . of the invention are used in assays to test samples of any given material to determine if the material includes ***prions*** which would infect another animal (such as a human) if the material were

ingested or injected. Standardized ***prion*** preparations of the invention are used to inoculate animals of the invention to create controls when carrying out an assay of the invention. The standardized ***prion*** preparation will always contain ***prions*** which will infect a genetically modified animal of the invention which animal will develop clinical signs of CNS dysfunction within. . .

SUMM . . . PrP gene which includes a portion of a gene of the animal (e.g. human) in danger of infection from ***prions*** in the sample. For example, Creutzfeldt Jakob Disease (CJD) is a fatal neurodegenerative disease of humans caused by ***prions*** . Preferred transgenic (Tg) mice disclosed herein express a chimeric ***prion*** protein (PrP) in which a segment of mouse (Mo) PrP was replaced with the corresponding human (Hu) PrP sequence. The. . . MHu2MPPrP, differs from MoPrP by 9 codons between codons 96 and 167. All of the Tg(MHu2MPPrP) mice injected with human ***prions*** developed neurologic disease. More specifically, the transgenic mice of the invention developed the disease .about.200 days after inoculation with brain homogenates from three CJD patients. When inoculated with CJD ***prions*** , MHu2MPPrP.sup.Sc was formed; in contrast MoPrP.sup.Sc was produced if Mo ***prions*** were inoculated. Tg(MHu2MPPrP) mice disclosed herein are useful in the diagnosis, prevention and treatment of human ***prion*** diseases. Transgenic mice containing the artificial PrP gene or elevated levels of expression of a native PrP gene from a genetically diverse animal can be used to test samples for ***prions*** which might infect such animals. The transgenic and hybrid animals disclosed herein consistently develop the adverse effects of such ***prions*** in a relatively short time and are substantially cheaper and easier to maintain than are currently used primate models. Transgenic mice containing a human ***prion*** protein gene are designated Tg(HuPrP) and may be crossed with mice with an ablated endogenous ***prion*** protein gene which are designated Prnp.sup.0/0 to obtain a hybrid designated Tg(HuPrP)/Prnp.sup.0/0.

SUMM . . . into the genome of one animal (e.g., a mouse, hamster or rat) will render the mammal susceptible to infections from ***prions*** which naturally only infect a genetically diverse mammal, e.g., human, bovine or ovine.

SUMM Another object of the invention is to provide an assay for the detection of ***prions*** in a sample.

SUMM Another object is to provide a hybrid animal which is obtained by crossing an animal having an ablated endogenous ***prion*** protein gene with a transgenic animal containing (1) a chimeric gene or (2) the ***prion*** protein gene of a genetically diverse animal which gene may be present at elevated levels.

SUMM Another object is to provide a standardized ***prion*** preparation produced from harvested brain tissue taken from animals of the invention (that have substantially identical genomes and specifically have substantially identical genetic material related to ***prions***) which animals exhibit symptoms of ***prion*** infection after being inoculated with ***prions*** which generally only infect a genetically diverse species.

SUMM A feature of the invention is that the standardized ***prion*** preparations of the invention can be used to consistently inoculate control animals with a known amount and type of ***prion*** .

SUMM . . . (e.g. a human, cow or sheep) in a manner so as to render the host animal susceptible to infection with ***prions*** which normally infect only the genetically diverse test animal.

SUMM . . . to the PrP gene of the genetically diverse animal which transgenic animal may be used by itself to assay for ***prions*** or for cross-breeding with an animal which has an ablated endogenous ***prion*** protein gene.

SUMM . . . of the present invention is that the transgenic and hybrid

animal can be used to assay for the presence of ***prions*** in a sample in a manner which is substantially faster, more efficient and cheaper than presently available assay methods.

SUMM Another advantage is that transgenic and hybrid animals inoculated with ***prions*** of humans can be used as test animals for testing drugs for efficacy in the treatment of humans suffering from diseases resulting from infection with ***prions***.

SUMM Another advantage is that the transgenic and hybrid animals can detect ***prions*** in a sample at very low levels, e.g., 1 part per million, and even as low as 1 part per . . .

SUMM . . . animals provide an assay which is highly accurate, i.e., does not provide false positives and consistently determines the presence of ***prions***.

SUMM Yet another advantage is that by increasing the copy number of an exogenous ***prion*** protein gene of the invention in a transgenic or hybrid and/or disrupting the endogenous gene of, the incubation time for ***prion*** caused disease is decreased.

SUMM Another advantage is that the standardized ***prion*** preparations of the invention can eliminate the need for extracting brain tissue from mammals which may have been infected with different types of ***prions*** and may each have a different genetic make up regarding genetic material related to ***prions***.

SUMM Another advantage is that assays of then invention can be carried out more reliably using the standardized ***prion*** preparations of the invention.

SUMM A feature of the present invention is that the transgenic and hybrid animals injected with a sample containing pathogenic ***prions*** will consistently develop the disease effects of the ***prions*** within a relatively short time, e.g. about 200 days +/-50 days after injection or less.

DETD Before the present artificial gene, assay methodology, standardized ***prion*** preparations, and transgenic and hybrid animals used in the assay are described, it is to be understood that this invention is not limited to particular assay methods, chimeric and artificial genes, ***prion*** preparation or transgenic and hybrid animals described, as such methods, genes, preparations, and animals may, of course, vary. It is. . .

DETD The term " ***prion*** " shall mean an infectious particle known to cause diseases (spongiform encephalopathies) in humans and animals. The term " ***prion*** " is a contraction of the words "protein" and "infection" and the particles are comprised largely if not exclusively of PrPSc molecules encoded by a PrP gene. ***Prions*** are distinct from bacteria, viruses and viroids. Known ***prions*** include those which infect animals to cause scrapie, a transmissible, degenerative disease of the nervous system of sheep and goats as well as bovine spongiform encephalopathies (BSE) or mad cow disease and feline spongiform encephalopathies of cats. Four ***prion*** diseases known to affect humans are (1) kuru, (2) Creutzfeldt-Jakob Disease (CJD), (3) Gerstmann-Strassler-Scheinker Disease (GSS), and (4) fatal familial insomnia (FFI). As used herein ***prion*** includes all forms of ***prions*** causing all or any of these diseases or others in any animals used--and in particular in humans and in domesticated. . .

DETD The terms "PrP gene" and " ***prion*** protein gene" are used interchangeably herein to describe genetic material which expresses proteins as shown in FIGS. 3-5 of U.S.. . .

DETD The terms "standardized ***prion*** preparation", " ***prion*** preparation", "preparation" and the like are used interchangeably herein to describe a composition containing ***prions*** which composition is obtained from brain tissue of mammals which contain substantially the same genetic material as relates to ***prions***, e.g., brain tissue from a set of mammals which exhibit signs of ***prion*** disease

which mammals (1) include a transgene of the invention; (2) have an ablated endogenous ***prion*** protein gene; (3) have a high copy number of ***prion*** protein gene from a genetically diverse species; or (4) are hybrids with an ablated endogenous ***prion*** protein gene and a ***prion*** protein gene from a genetically diverse species. The mammals from which standardized ***prion*** preparations are obtained exhibit clinical signs of CNS dysfunction as a result of inoculation with ***prions*** and/or due to developing the disease due to their genetically modified make up, e.g., high copy number of ***prion*** protein genes.

DETD The term "PrP gene" refers generally to any gene of any species which encodes any form of a ***prion*** protein. Some commonly known PrP sequences are described in Gabriel et al., Proc. Natl. Acad. Sci. USA 89:9097-9101 (1992) which. . .

DETD . . . when included in the genome of a host animal (e.g., a mouse) will render the mammal susceptible to infection from ***prions*** which naturally only infect a genetically diverse test mammal, e.g., human, bovine or ovine. In general, an artificial gene will. . . codon of a genetically diverse mammal (such as a human). The genetically altered mammal being used to assay samples for ***prions*** which only infect the genetically diverse mammal. Examples of artificial genes are mouse PrP genes encoding the sequence as shown. . . associated with any native PrP gene but which, when inserted into an animal render the animal susceptible to infection with ***prions*** which would normally only infect a genetically diverse animal.

DETD The terms "chimeric gene," "chimeric PrP gene", "chimeric ***prion*** protein gene" and the like are used interchangeably herein to mean an artificially constructed gene containing the codons of a . . . will, when inserted into the genome of a mammal of the host species, render the mammal susceptible to infection with ***prions*** which normally infect only mammals of the second species. The preferred chimeric gene disclosed herein is MHu2M which contains the. . .

DETD The term "genetic material related to ***prions*** " is intended to cover any genetic material which effects the ability of an animal to become infected with ***prions*** . Thus, the term encompasses any "PrP gene", "artificial PrP gene", "chimeric PrP gene" or "ablated PrP gene" which terms are defined herein as well as modification of such which effect the ability of an animal to become infected with ***prions*** . Standardized ***prion*** preparations of the invention are produced using animals which all have substantially the same genetic material related to ***prion*** so that all of the animals will become infected with the same type of ***prions*** and will exhibit signs of infection at about the same time.

DETD . . . may be any animal for which one wishes to run an assay test to determine whether a given sample contains ***prions*** with which the test animal would generally be susceptible to infection. For example, the test animal may be a human, cow, sheep, pig, horse, cat, dog or chicken, and one may wish to determine whether a particular sample includes ***prions*** which would normally only infect the test animal. This is done by including PrP gene sequences of the test animal into the host animal and inoculating the host animal with ***prions*** which would normally only infect the test animal.

DETD The terms "ablated ***prion*** protein gene", "disrupted PrP gene", and the like are used interchangeably herein to mean an endogenous ***prion*** protein gene which has been altered (e.g., add and/or remove nucleotides) in a manner so as to render the gene inoperative. Examples of non-functional ***prion*** protein genes and methods of making such are disclosed in Bueler, H., et al "Normal development of mice lacking the. . .

DETD . . . are used interchangeably herein to mean an animal obtained from the cross-breeding of a first animal having an ablated endogenous

prion protein gene with a second animal which includes either (1) a chimeric gene or artificial ***prion*** protein gene or (2) a ***prion*** protein gene from a genetically diverse animal. For example a hybrid mouse is obtained by cross-breeding a mouse with an ablated mouse ***prion*** protein gene with a mouse containing (1) human ***prion*** protein genes (which may be present in high copy numbers) or (2) chimeric genes. The term hybrid includes any offspring of a hybrid including inbred offspring of two hybrids provided the resulting offspring is susceptible to infection with ***prions*** with normal infect only a genetically diverse species.

DETD The terms "susceptible to infection" and "susceptible to infection by ***prions***" and the like are used interchangeably herein to describe a transgenic or hybrid test animal of the invention which has. . . 80% or greater, preferably 98% or greater, and most preferably a 100% chance of developing a disease if inoculated with ***prions*** which would normally only infect a genetically diverse test animal. The terms are used to describe a transgenic or hybrid. . . as a transgenic mouse Tg(MHu2M) which, without the chimeric PrP gene, would not be susceptible to infection with a human ***prion*** (less than 20% chance of infection) but with the chimeric gene is susceptible to infection with human ***prions*** (80% to 100% chance of infection).

DETD The term "incubation time" shall mean the time from inoculation of an animal with a ***prion*** until the time when the animal first develops detectable symptoms of disease resulting from the infection. A reduced incubation time. . .

DETD HuPrP for a human ***prion*** protein;

DETD MoPrP for a mouse ***prion*** protein;

DETD SHaPrP for a Syrian hamster ***prion*** protein;

DETD PrP.sup.Sc for the scrapie isoform of the ***prion*** protein;

DETD MoPrP.sup.Sc for the scrapie isoform of the mouse ***prion*** protein;

DETD Prn-p.sup.0/0 for ablation of both alleles of an endogenous ***prion*** protein gene, e.g., the MoPrP gene;

DETD Tg(HuPrP)/Prmpo.sup.0/0 for a hybrid mouse obtained by crossing a mouse with a human ***prion*** protein gene (HuPrP) with a mouse with both alleles of the endogenous ***prion*** protein gene disrupted;

DETD Tg(MHu2M)/Prnp.sup.0/0 for a hybrid mouse obtained by crossing a mouse with a chimeric ***prion*** protein gene (MHu2M) with a mouse with both alleles of the endogenous ***prion*** protein gene disrupted.

DETD . . . into the genome of a host animal (e.g. a mouse or hamster) will render the animal susceptible to infection with ***prions*** which normally infect only a genetically diverse test animal (e.g. a human, cow or sheep), thereby including genes wherein one. . . is replaced with a corresponding portion of a human PrP gene thereby rendering the mouse susceptible to infection with human ***prions*** ; (4) a transgenic mammal with elevated levels of expression of a PrP gene of a genetically diverse mammal wherein the. . . a genetically diverse animal; (5) a transgenic hybrid animal which is obtained by crossing a animal having an ablated endogenous ***prion*** protein gene with an animal with a chimeric gene as per (2) above or an animal with a ***prion*** protein gene of another genetically diverse animal therein e.g., as per (4) above; (6) standardized ***prion*** preparations which contain the same amount and type off ***prions*** in each preparation; (7) a method of determining whether a sample is infected with ***prions*** which method involves inoculating a transgenic or hybrid mammal of the invention with a sample to be tested (and preferably simultaneously inoculating identical test animals with a standardized ***prion*** preparation for use as controls) and observing the mammal(s) for a period of time sufficient to determine if the mammal(s) develop(s) symptoms of a disease normally associated with ***prions*** ; (8) a method of testing the efficacy of a drug in the

treatment of disease developed as a result of infection with ***prions*** comprising administering a drug to be tested to a transgenic or hybrid animal infected with ***prions*** (preferably a standardized ***prion*** preparation) and observing and/or testing the mammal to determine if the drug aids in treating or slowing the progress of. . . as extracted brain tissue from the animal which has died (and preferably inoculating control animals with a standardized preparation of ***prions***) and observing the transgenic or hybrid animal (and control animals) in order to determine if the animal(s) develop(s) symptoms of ***prion*** infections.

DETD . . . of the invention is to use the animal to test a sample of material to determine if that material has ***prions*** which will infect a human and cause a human to develop a CNS disease such as CJD.

DETD . . . some instances. More specifically, due to small differences in the protein encoded by the PrP gene of different mammals, a ***prion*** which will infect one mammal (e.g. a human) will not normally infect a different mammal (e.g. a mouse). Due to. . . it is not generally possible to use normal animals, (i.e., animal which have not had their genetic material related to ***prions*** manipulated) such as mice to determine whether a particular sample contains ***prions*** which would normally infect a different species of animal such as a human. The present invention solves this problem in. . .

DETD . . . order for the transgenic animals to be useful, it is necessary for the animals to be susceptible to infection with ***prions*** which normally infect only genetically diverse test animals, and in particular animals of commercial significance for testing, such as humans,. . .

DETD . . . the resulting transgenic animal (with a low copy number of human PrP genes) is not susceptible to infection with human ***prions***. Second, we found that infection would occur if the endogenous PrP gene of the host animal is ablated. Third, when. . . codons differing between the host and the test animal are switched, the resulting transgenic animal is susceptible to infection with ***prions*** which normally only infect the test animal.

DETD . . . with the PrP gene of a test animal to obtain a useful transgenic animal which is susceptible to infection with ***prions*** which normally only infect the test animal by substantially increasing the copy number of the test animal's PrP gene in. . . of a human in a relatively low copy number (e.g. 1 to 4) is not susceptible to infection with human ***prions*** (unless the endogenous mouse PrP gene is ablated). However, if the transgenic mouse includes a very high copy number of a human gene (e.g. 30-300 copies), the resulting transgenic animal is susceptible to infection with human ***prions***. Further, when a host animal such as a mouse has only a portion of its PrP gene replaced with a. . . corresponding portion of a test animal such as a human, the resulting transgenic animal is highly susceptible to infection with ***prions*** which normally infect only the test animal. This is true even if the chimeric gene is present in the transgenic. . .

DETD Lastly, in order to reduce incubation time hybrid mice were created by crossing mice with ablated ***prion*** protein genes with transgenic mice which (1) included a ***prion*** protein gene from a genetically diverse animal e.g., a human or (2) include a chimeric or artificial gene of the. . . the copy number is not increased so far that the animal becomes spontaneously ill, i.e., become ill without inoculation with ***prions***.

DETD . . . the copy number tends to decrease the incubation time for the disease once the animal is inoculated with material containing ***prions***. Notwithstanding such, we now understand that, when the copy number is increased to very high numbers (e.g. 100 copies and above), the transgenic animals may spontaneously demonstrate symptoms of

prion disease. Thus, a most preferred transgenic animal of the invention will include a chimeric PrP gene in a sufficiently high. . . time (e.g. 50 copies \pm .25) but in a sufficiently low number so as to not initiate spontaneous symptoms characteristic of ***prion*** diseases (e.g., not more than 100 copies). It will be understood by those skilled in the art that the number. . . adjustments can be made to increase the copy number if the resulting transgenic animals are not subject to infection with ***prions*** which normally infect only a genetically diverse animal. Further, adjustments can be made with respect to the use of specific. . .

DETD . . . the entire PrP gene sequence of the test animal into the host animal and render the host animal susceptible to ***prions*** which normally only infect the test animal. However, such is not the case when the host animal and test animal. . . PrP gene, such as that of a human, the resulting transgenic mouse will not be susceptible to infection with human ***prions*** unless (1) the endogenous PrP gene of the mouse is ablated or (2) the human gene is present in the. . .

DETD . . . that the animal would not spontaneously become sick, and yet allow the animal to become sick when inoculated with human ***prions***, we created a chimeric gene which includes only a portion of the human PrP gene in the mouse PrP gene.. . .

DETD When transgenic animals are produced by placing the entire human ***prion*** protein gene into that of a mouse the resulting transgenic mouse does not become consistently ill in a short period of time when inoculated with ***prions*** which generally only infect humans i.e., is not susceptible to infection with human ***prions***. The inability to become infected appears to be related to the presence of the endogenous mouse ***prion*** protein gene. When a mouse with a human ***prion*** protein gene is crossed with a mouse with a disrupted endogenous mouse gene the hybrid offspring are infected by ***prions*** which normally only infect humans. Such hybrid mice will consistently become infected and exhibit an incubation time of less than. . .

DETD . . . with a long incubation time. While the high cost of caring for nonhuman primates prevented extensive studies of the human ***prion*** diseases, the transmissibility of these diseases stimulated studies of the animal ***prion*** analogues in rodents [Manuelidis et al., Proc. Natl. Acad. Sci. USA 75:3422-3436 (1978); Manuelidis et al., Proc. Natl. Acad. Sci.. . .

DETD The present disclosure opens a new frontier in the investigation of the human ***prion*** diseases since transmission studies can now be performed relatively rapidly in genetically altered mammals such as Tg(MHu2M) mice that are relatively inexpensive to maintain. For the first time, endpoint titrations of ***prions*** in multiple human body tissues and fluids can be performed and standard curves constructed for more economical incubation time assays. The information derived from such studies of human ***prions*** will be useful in the management of CJD patients who are thought to pose some risk to relatives, physicians, nurses. . .

DETD In studies of human ***prion*** diseases with apes and monkeys, the use of one or two, or rarely three, animals as recipients for a single. . . significant problem in evaluating the transmissibility of a particular inoculum from an individual patient. The transgenic mice contain a chimeric ***prion*** protein gene, e.g., Tg(MHu2M) mice, and hybrid mice e.g., Tg(HuPrP)/Pmp.sup.0/0 described here obviate many of the problems created by using. . .

DETD These results demonstrate the "universality" of the MHu2M transgene for transmission studies with other types of transgenic animals and other ***prion*** inocula. For example, it may be most efficient to use mice expressing MHu2MPPrP transgenes coding for either a methionine or. . .

DETD . . . PrP gene which, when inserted into a host mammal (such as a

mouse) renders that mammal susceptible to infection with ***prions*** which normally infect only a genetically diverse test mammal (e.g. a human, cow or sheep). The artificial PrP gene may. . .

DETD . . . segments of the human PrP gene and obtain a transgenic mouse which is subject to being readily infected with human ***prions***. Thus, the invention is not limited to the particular chimeric gene MHu2M or chimeric mice produced using this gene. The. . . types of transgenic animals which include artificial genes wherein the artificial gene renders the transgenic animal susceptible to infection with ***prions*** which normally infect only a genetically diverse animal.

DETD . . . break the "species barrier" by creating a particular chimeric gene whereby transgenic mice can test for the presence of human ***prions*** we have opened the door for the creation of other transgenic animals which will include other artificial PrP genes which, for example, can allow for the testing for the presence of bovine or ovine ***prions*** in a sample.

DETD Hybrid animals of the invention can be produced by crossing an animal with an ablated endogenous ***prion*** protein gene with either of the transgenic animals mentioned above. For example, a mouse containing a human/mouse chimeric ***prion*** is crossed with a mouse with a disrupted endogenous ***prion*** protein gene e.g., Tg(Pmp.sup.0/0). Alternatively, a mouse containing a high copy number of human ***prion*** protein genes (e.g., 50.+-.25) is crossed with a mouse with a disrupted endogenous ***prion*** protein gene e.g., Tg(Pmp.sup.0/0) to obtain a hybrid Tg(HuPrP)/Pmp.sup.0/0. A variety of different hybrids can be obtained by crossing an animal with an ablated ***prion*** protein gene (i.e., a null ***prion*** background) with different transgenic animals with different ***prion*** protein genes. When successful hybrids are obtained they can be crossed to produce other animals which for the purpose of the disclosure are also considered hybrids if they are susceptible to infection with ***prions*** which generally only infect a genetically diverse species. A null ***prion*** background means that more than 50% of the endogenous ***prion*** protein genes are disrupted, preferable more than 80%, more preferable more than 90% and most preferable 100%.

DETD The incubation time of Tg(MHu2M) mice inoculated with Hu ***prions*** is now about 200 days or less .+-.50 days, which can be reduced substantially by increasing the copy number of. . . transgene expression was found to be inversely proportional to the length of the scrapie incubation time after inoculation with SHa ***prions*** [Prusiner et al., Cell 63:673-686 (1990)]. Thus, producing Tg(MHu2M) mice with higher levels of transgene expression is a means of. . .

DETD . . . substitutions in other chimeric Hu/Mo PrP constructs, it is possible to further enhance the susceptibility of Tg mice to Hu ***prions*** as reflected by shortened incubation times. Shortening the incubation time is a worthwhile goal for the facilitation of many future studies in ***prion*** research and for the evaluation of pharmaceuticals, foods, tissues, organs, grafts, cosmetics and other substances--particularly substances which have some portion derived from an animal, such as a human, which animal might be infected with ***prions***.

DETD . . . of a chimeric or artificial PrP gene and the incubation time of disease after inoculation of the transgenic animal with ***prions***. Specific MHu2M mice disclosed herein have only 3 or 4 copies of the MHu2M gene. The number of copies can. . .

DETD . . . PrP genes have been determined allowing, in each case, the prediction of the complete amino acid sequence of their respective ***prion*** proteins. The normal amino acid sequence which occurs in the vast majority of individuals is referred to as the wild-type. . . either five or six repeats of an eight amino acid motif sequence in the amino terminal region of the mature ***prion*** protein. While none

of these polymorphisms are of themselves pathogenic, they appear to influence ***prion*** diseases. Distinct from these normal variations of the wild-type ***prion*** proteins, certain mutations of the human PrP gene which alter either specific amino acid residues of PrP or the number of octarepeats have been identified which segregate with inherited human ***prion*** diseases.

DETD The fundamental event in ***prion*** propagation seems to be the conversion of PrP^{sup.C}, which contains .about.43% .alpha.-helix and is devoid of .beta.-sheet, into PrP^{sup.Sc} which. . . feature in the formation of PrP^{sup.Sc}. One explanation for the difference in susceptibility of Tg(MHu2M) and Tg(HuPrP) mice to Hu ***prions*** in mice may be that mouse chaperons catalyzing the refolding of PrP^{sup.C} into PrP^{sup.Sc} can recognize MHu2MPrP much more readily. . .

DETD . . . In support of this hypothesis is that rodents also differ from ruminants including sheep and cattle at this site; sheep ***prions*** have failed to transmit neurodegeneration to Tg(ShePrP). In these experiments the transgenic mice expressed the entire sheep PrP gene.

DETD In contrast to Tg(MHu2M) mice, the overall transmission rate of Hu ***prion*** inocula from a wide variety of sources was less than 10% in Tg(HuPrP) mice, no different from the rate observed. . . appears to be a relatively infrequent event similar to the rare conversion of MoPrP^{sup.C} to PrP^{sup.Sc} in response to human ***prions***. The low rates of transmission in these mice do not seem to be a consequence of low titers of human ***prion*** titers: two inocula which failed to cause disease in Tg(HuPrP) mice transmitted to 100% of inoculated Tg(MHu2M) animals.

DETD . . . in the presence of MoPrP^{sup.C} and why HuPrP^{sup.C} is converted into PrP^{sup.Sc} in the absence of MoPrP^{sup.C}. This model of ***prion*** propagation involving protein X can also explain why inherited forms of ***prion*** disease modeled in mice with the GSS mutation at codon 102 can be produced with Tg mice expressing the P102L. . . HuPrP as described here. The proposed model is consistent with additional observations showing that Tg(MHu2M) mice were resistant to Hu ***prions*** from a patient with GSS who carried the P102L mutation but were susceptible to ***prions*** from patients with familial CJD who harbor the E200K mutation; however, Tg(MHu2M-P101L) mice were susceptible to GSS ***prions***. These findings and other studies reported here demonstrate that single amino acid mismatches at codon 102 or 129 prolong the. . .

DETD "Strains" of Human ***Prions***

DETD Studies in rodents have shown that ***prion*** strains produce different patterns of PrP^{sup.Sc} accumulation [Hecker et al., Genes & Development 6:1213-1228 (1992); DeArmond et al., Proc. Natl. . . by the sequence of PrP^{sup.C} [Carlson et al., Proc. Natl. Acad. Sci. USA in press (1994)]. The molecular basis of ***prion*** diversity has for many years been attributed to a scrapie specific nucleic acid [Bruce et al., J. Gen. Virol. 68:79-89. . . [Meyer et al., J. Gen. Virol. 72:37-49 (1991); Kellings et al., J. Gen. Virol. 73:1025-1029 (1992)]. Other hypotheses to explain ***prion*** strains include variations in PrP Asn-linked sugar chains [Hecker et al., Genes & Development 6:1213-1228 (1992)] and multiple conformers of. . .

DETD The patterns of PrP^{sup.Sc} accumulation in the brains of inoculated Tg(MHu2M) mice were markedly different for RML ***prions*** and Hu ***prions***. However, RML ***prion*** inocula containing MoPrP^{sup.Sc} stimulated the formation of more MoPrP^{sup.Sc} while Hu ***prion*** inocula containing HuPrP^{sup.C} triggered production of MHu2MPrP^{sup.Sc}. The distribution of neuropathological changes characterized by neuronal vacuolation and astrocytic gliosis is similar to the patterns of PrP^{sup.Sc} accumulation in the brains of Tg(MHu2M) mice inoculated with RML ***prions*** or Hu ***prions***.

DETD New Approaches To Investigating Human ***Prion*** Diseases

DETD The remarkable sensitivity of Tg(MHu2M) mice to Hu ***prions*** represents an important advance in neurodegenerative disease research.

Based on the present disclosure regarding chimeric Hu/Mo PrP transgenes we conceived of a similar approach to the construction of Tg mice susceptible to BSE and scrapie sheep ***prions***. Such would be useful in detecting ***prion*** diseases in domestic animals. The importance of animal ***prion*** diseases is illustrated by BSE or "mad cow disease" in Great Britain, where >150,000 cattle have died. This ***prion*** disease BSE is thought to have originated with cattle consuming meat and bone meal produced from sheep offal containing scrapie ***prions*** [Wilesmith, J. W., Semin. Viro. 2:239-245].

DETD . . . sheep scrapie about the risk factors to humans from BSE.

Whether any of these seven amino acid substitutions render bovine ***prions*** permissive in humans remains to be established. It may be that Tg(MHu2M) mice are susceptible to bovine as well as sheep ***prions***. Of perhaps even greater importance, Tg(MHu2M) mice have immediate application in the testing of pharmaceuticals for human ***prion*** contamination. The Tg(MHu2M) mice described here provide a sensitive, reliable and economical bioassay for detecting the presence of human ***prions***.

DETD Standardized ***Prion*** Preparation

DETD Standardized ***prion*** preparations are produced for use in assays so as to improve the reliability of the assay. Although the preparation can be obtained from any animal it is preferably obtained from a host animal which has brain material containing ***prions*** of a test animal. For example, a Tg mouse containing a human ***prion*** protein gene can produce human ***prions*** and the brain of such a mouse can be used to create a standardized human ***prion*** preparation. Further, in that the preparation is to be a "standard" it is preferably obtained from a battery (e.g., 100; . . . and mutations) would spontaneously develop disease and the brain tissue from each could be combined to make a useful standardized ***prion*** preparation.

DETD Standardized ***prion*** preparations can be produced using any of the modified host mammals of the present invention. For example, standardized ***prion*** preparations could be produced using mice, rats, hamsters, or guinea pigs which are genetically modified per the present invention so that they are susceptible to infection with ***prions*** which ***prions*** would generally only infect genetically diverse species such as a human, cow, sheep or horse and which modified host mammals. . . will develop clinical signs of CNS dysfunction within a period of time of 350 days or less after inoculation with ***prions***. The most preferred host mammal is a mouse in part because they are inexpensive to use and because a greater.

DETD . . . mouse, the next step is to choose the appropriate type of genetic manipulation to be utilized to produce a standardized ***prion*** formulation. For example, the mice may be mice which are genetically modified by the insertion of a chimeric gene of. . . PrP genes into the genome so as to create mice which are susceptible to infection with a variety of different ***prions***, i.e., which generally infect two or more types of test animals. For example, a mouse could be created which included. . . types of chimeric genes were inserted into the genome of the mouse the mouse would be susceptible to infection with ***prions*** which generally only infect a human, cow and sheep.

DETD . . . is to produce a large number of such mammals which are substantially identical in terms of genetic material related to ***prions***. More specifically, each of the mice produced will include an identical chimeric gene present in the genome in substantially the same copy number. The mice should be sufficiently identical genetically in terms of genetic material related to

prions that 95% or more of the mice will develop clinical signs of CNS dysfunction within 350 days or less after. . .

DETD . . . still more preferably 500 or more of such mice are produced.

The next step is to inoculate the mice with ***prions*** which generally only infect a genetically diverse mammal e.g., ***prions*** from a human, sheep, cow or horse. The amounts given to different groups of mammals could be varied. After inoculating the mammals with the ***prions*** the mammals are observed until the mammals exhibit symptoms of ***prion*** infection e.g., clinical signs of CNS dysfunction. After exhibiting the symptoms of ***prion*** infection the brain or at least a portion of the brain tissue of each of the mammals is extracted. The extracted brain tissue is homogenized which provides the standardized ***prion*** preparation.

DETD As an alternative to inoculating the group of transgenic mice with ***prions*** from a genetically diverse animal it is possible to produce mice which spontaneously develop ***prion*** related diseases. This can be done, for example, by including extremely high copy numbers of a human PrP gene into. . . 100 or more copies, the mouse will spontaneously develop clinical signs of CNS dysfunction and have, within its brain tissue, ***prions*** which are capable of infecting humans. The brains of these animals or portions of the brain tissue of these animals can be extracted and homogenized to produce a standardized ***prion*** preparation.

DETD The standardized ***prion*** preparations of the invention can be used directly or can be diluted and titrated in a manner so as to. . . second set of substantially identical mice are inoculated with a material to be tested i.e., a material which may contain ***prions***. A third group of substantially identical mice are not injected with any material. The three groups are then observed. The. . . is also inaccurate probably because the mice have not been correctly created so as to become ill when inoculated with ***prions*** which generally only infect a genetically diverse mammal. However, if the first group does become ill and the third group. . . be presumed to be accurate. Thus, if the second group does not become ill the test material does not contain ***prions*** and if the second group does become ill the test material does contain ***prions***.

DETD By using standardized ***prion*** preparations of the invention it is possible to create extremely dilute compositions containing the ***prions***. For example, a composition containing one part per million or less or even one part per billion or less can. . . composition can be used to test the sensitivity of the transgenic mice of the invention in detecting the presence of ***prions*** in the sample.

DETD ***Prion*** preparations of the present invention are desirable in that they will include a constant amount of ***prions*** and are extracted from an isogenic background. Accordingly, contaminants in the preparations will be constant and controllable. Standardized ***prion*** preparations of the invention will be useful in the carrying out of bioassays in order to determine the presence, if any, of ***prions*** in various pharmaceuticals, whole blood, blood fractions, foods, cosmetics, organs and in particular any material which is derived from an animal (living or dead) such as organs, blood and products thereof derived from living or dead humans. Thus, standardized ***prion*** preparations of the invention will be valuable in validating purification protocols where preparations are spiked and reductions in titer measured. . .

DETD Since the fundamental event underlying ***prion*** propagation seems to be a conformational change in PrP [Pan et al., Proc. Natl. Acad. Sci. USA 90:10962-10966 (1993)] and. . . positions out of 254 [Kretzschmar et al., DNA 5:315-324 (1986)], we constructed modified PrP transgenes. Chimeric SHa/Mo transgenes have produced ***prions*** with new

properties, the most useful being the chimeric SHa/Mo transgene labeled MHu2M which carries 5 amino acid substitutions found. . .

DETD Mice expressing the MHu2M chimeric transgene are susceptible to human ***prions*** after abbreviated incubation times. More specifically, the transgenic mice of the present invention which include the chimeric MHu2M gene will, after inoculation with human ***prions***, develop disease symptoms attributed to the ***prions*** within about 200 days +/-50 days. Further, 80% or more the transgenic mice of the invention inoculated with human ***prions*** will develop symptoms of the disease, more preferably 98% or more of the mice will develop symptoms of the disease. According to experiments carried out, 100% of the transgenic MHu2M mice inoculated with human ***prions*** actually developed symptoms of the disease in about 200 days or less +/-50 days.

DETD . . . neurodegeneration more rapidly than monkeys, they provide a preferred host for bioassays of infectivity in tissues of humans dying of ***prion*** diseases. The Tg(MHu2M) mice disclosed herein provide an excellent system for assessing the sterility of pharmaceuticals as well as tissue and organ grafts prepared from human sources. Other transgenic mice which include the ***prion*** protein gene of the animal in danger of infection can be used to test samples for ***prion*** diseases which can infect domestic animals such as sheep and cattle.

DETD . . . PrP genes can be created which, when inserted into a host animal, will render that animal susceptible to infection with ***prions*** which normally only infect a second and genetically diverse test animal. There are nearly an infinite number of possible artificial. . . would meet the basic criteria of the invention, i.e. rendering a mammal such as a mouse susceptible to infection with ***prions*** which normally infect only a genetically diverse test animal such as a human. The MHu2M gene of the invention is. . . are included. Transgenic mice expressing only low levels of human PrP.sup.C are unlikely to become ill after inoculation with human ***prions***. However, if the level of human PrP.sup.C expression is elevated, the transgenic animals become susceptible to infection with human ***prions***. This is another means of overcoming the species barrier by what is referred to as a stochastic process.

DETD . . . the resulting gene could be inserted into a mouse in order to render the mouse susceptible to infection with bovine ***prions***. A similar strategy with respect to producing a mouse which would be susceptible to infection with sheep ***prions*** can be deduced from reviewing FIG. 5 of U.S. Pat. No. 5,565,186. In addition to these possibilities those skilled in. . . to obtain a useful artificial gene which, when inserted into an animal, will render that animal susceptible to infection with ***prions*** which normally would infect only a genetically diverse mammal.

DETD . . . mammal will express the PrP gene at a level sufficiently high to render the host animal susceptible to infection with ***prions*** which normally only infect a genetically diverse test animal.

DETD PrP.sup.Sc has been found in the brains of affected Tg(MHu2M) mice after inoculation with Hu(CJD) or Mo(RML) ***prions***. Brain homogenates of Tg(MHu2M) were either left undigested or digested with proteinase K (BMB) at a final concentration of 20. . .

DETD The distribution of PrP.sup.C and PrP.sup.Sc in clinically sick Tg(MHu2M) mice inoculated with Mo(RML) and Hu(CJD) ***prions*** were detected by the histoblot method. The histoblots included those of coronal sections through the region of the hippocampus and. . .

DETD . . . of these offspring. As shown in Example 5 below, these mice were found to be susceptible to infection with human ***prions*** 100% of the time.

DETD Sources of ***Prion*** Inocula

DETD . . . clinical diagnosis of CJD or GSS had been confirmed by histopathological examination of brain tissues and, in most cases, by ***prion*** protein analysis. In some cases, the PrP gene was amplified by PCR of DNA isolated from patient blood and the . . .

DETD . . . to X-ray film for 5-60 seconds. alpha-PrP RO73 rabbit antiserum was used at a final dilution of 1:5000 and 3F4 ***monoclonal*** antibody was also employed [Serban et al., Neurology 40:110-117 (1990)].

DETD Tg(MHu2MPPrP) Mice Are Susceptible to Human ***Prions***

DETD Inoculation of Tg(MHu2M) mice with Mo(RML) ***prions*** passaged in mice produced disease in 178.+-.3 days, which is .about.40 longer than Mo(RML) ***prions*** in non-Tg mice. Prolongation of incubation times in mice expressing non-murine transgenes is well established, and occurs presumably because the . . . conversion of MoPrP.sup.C into MoPrP.sup.Sc [Prusiner et al., Cell 63:673-686 (1990)]. In contrast to Tg(MHu2M) mice, incubation times for RML ***prions*** in Tg(MH2M) mice were the same as those of the non-Tg mice [Scott et al., Cell 73:979-988 (1993)].

DETD TABLE 1

Incubation of human (CJD) and mouse (RML) ***prion*** inocula in Tg(MHu2M)FVB-B5378 mice
Incubation Times
(mean days .+-. SE)
Range
Source Inoculum No..sup.a
(days) Illness
Death.sup.b

Sporadic

RG	8/8	225-249
		238 .+-. 3.2
		240. . .

DETD Tg(HuPrP) Mice Are Resistant to Human ***Prions***

DETD To determine whether expression of HuPrP in Tg(HuPrP)B6SJL-110 and Tg(HuPrP)FVB-152 conferred susceptibility to human ***prions***, incubation periods were measured after inoculation of Tg(HuPrP) and non-Tg mice with brain extracts from 18 patients that had died. . . 2.5 years, we concluded that the two lines of Tg(HuPrP) mice were no more responsive than non-Tg mice to human ***prions*** (see Table 2 below). The rate of transmission to Tg(HuPrP) mice was 8.3% (14 clinically sick mice out of 169. . . after extremely long incubation periods is compounded by the heightened potential for artifactual results due to low levels of contaminating ***prions*** .

DETD Statistical analysis shows that the frequency of Hu ***prion*** transmission to Tg(MHu2MPPrP) mice compared to Tg(HuPrP) and non-Tg mice is highly significant using the Fisher's exact test, $p < 10^{-7}$ [Mehta et al., J. Am. Stat. Assn. 78:(392) 427-434 (1983)]. When Hu ***prion*** transmission to Tg(HuPrP) mice was compared to non-Tg mice, the frequencies were similar, $p = 0.79$.

DETD To confirm the clinical diagnosis of ***prion*** disease, 5 ill Tg(HuPrP) and 1 non-Tg mice were sacrificed and brain extracts were examined for the presence of PrP.sup.Sc. . . mice which developed clinical signs after 589 days post-inoculation with iatrogenic CJD inoculum #170. The equivalent transmission rates of human ***prions*** in Tg(HuPrP) and non-Tg mice indicate that this is a rare event with the same frequency of occurrence as the stochastic conversion of MoPrP.sup.C to MoPrP.sup.Sc induced by human ***prions*** .

DETD . . . 3F4-reactive PrP.sup.Sc in the brains of 3 out of the 6 mice analyzed may reflect the difficulty of accurately diagnosing ***prion*** disease in elderly animals. Some of the mice inherited

prion diseases of both humans and Tg mice exhibit little or undetectable levels of protease-resistant PrP; yet, based on transmission studies, their brains contain ***prions*** and they show clear spongiform degeneration [Medori et al., N. Engl. J. Med. 326:444-449 (1992)].

DETD In contrast to Tg(MHu2M) mice, Hu ***prions*** from patient RG have not transmitted to either Tg(HuPrP) or non-Tg mice after >330 days (see Table 2 below). Attempts to transmit preparations enriched for Hu ***prion*** rods prepared from the brain of patient RG have likewise been negative for >300 days. In addition, inoculum from the. . .

DETD TABLE 2

Incubation times in Tg(HuPrP)FVB-152 and Tg(HuPrP)B6SJL-110 mice after inoculation with brain extracts from patients with human ***prion*** diseases

Host	Inoculum	Incubation times (n/.sub.a n.sub.o) (days .+-. SE).sup.b
Tg152	Sporadic CJD(#87011)	1/10 706
Non-Tg	Sporadic CJD(#87011)	3/5 697.3 .+-. 51
Tg 152	Sporadic. . .	

DETD Some clinically sick Tg(MHu2M) mice inoculated with each of the three CJD ***prion*** inocula or RML ***prions*** were sacrificed for histopathological verification of disease and for ***prion*** protein analysis. Western blots of brain homogenates from Tg(MHu2M) mice infected with Hu ***prions*** probed with RO73 and 3F4 .alpha.-PrP antibodies revealed the presence of protease-resistant PrP.sup.Sc which reacted with the 3F4 ***monoclonal*** antibody showing this protease-resistant product to be MHu2M PrP.sup.Sc. The epitope recognized by this antibody consists of a pair of. . . with MHu2MPrP.sup.Sc as well as HuPrP.sup.C and HuPrP.sup.Sc from diseased human brains. Brain homogenates from Tg(MHu2M) mice infected with RML ***prions*** contained PrP.sup.Sc which was detectable only with RO73 and not 3F4 .alpha.-PrP antibodies, indicating that Tg(MHu2M) mice are capable of producing MoPrP.sup.Sc but not MHu2MPrP.sup.Sc in response to RML ***prions*** previously passaged in mice. While these findings are similar to those reported for Tg(SHaPrP) mice [Scott et al., Cell 59:847-857 (1989)], they contrast with those found for Tg(MH2MPrP) mice where MH2MPrP.sup.Sc was formed in response to RML ***prions*** [Scott et al., Cell 73:979-988 (1993)].

DETD . . . histoblots of coronal brain sections through the hippocampus and thalamus of Tg(MHu2M) mice inoculated with RML or CJD ***prions***. The weak immunoreactivity of MHu2M PrP with RO73 permitted a degree of analysis which had not been previously possible in. . . react with this antibody. The pattern of PrP.sup.Sc deposition was highly dependent upon the species of origin of the infectious ***prions***. When inoculated with RML ***prions***, histoblots of the brains of Tg(MHu2M) were similar to those of CD-1 mice infected with RML ***prions***, revealing a diffuse pattern of MoPrP.sup.Sc deposition in the hippocampus, thalamus, hypothalamus and all layers of the neocortex. The histoblot pattern of was strikingly different for Tg(MHu2M) mice inoculated with CJD ***prions***. The deposition of MHu2MPrP.sup.Sc was confined primarily to the deep layers of the neocortex, the thalamus, particularly the ventral posterior. . . signal. The same pattern of MHu2MPrP.sup.Sc deposition was consistently observed in histoblots of Tg(MHu2M) mice inoculated with

all three CJD ***prion*** isolates prepared from human brain. It is noteworthy that the pattern of MHu2MPrP.sup.Sc deposition is similar to the pattern of. . . Natl. Acad. Sci. USA 89:7620-7624 (1992)]. The spongiform degeneration in the brains of Tg(MHu2M) mice infected with Mo(RML) and Hu(CJD) ***prions*** reflected the patterns of PrP.sup.Sc accumulation described above.

DETD . . . methods are listed in Tables 3-7. With respect to such the (1) methods of making mice; (2) brain homogenates; (3) ***prion*** inocula; (4) measurement of incubation times; (5) immunoblotting; and (6) immunohistochemistry are described below.

DETD . . . at codon 102 of the human PrP gene has been described Hsiao, K. and Prusiner, S. B. (1990). Inherited human ***prion*** diseases. Neurology 40:1820-1827. ORF cassettes were digested with BglII (which cleaves immediately adjacent to the initiation codon). The 5' protruding. . . to the Sall-cut cosSHa.Tet cosmid expression vector Scott, M. R., Kohler, R., Foster, D., and Prusiner, S. B. (1992). Chimeric ***prion*** protein expression in cultured cells and transgenic mice. Protein Sci. 1:986-997. The isolation of recombinant cosmid clones was achieved by. . . Scott, M., Groth D., Foster, D., Torchia, M., Yang, S.-L., DeArmond, S. J., and Prusiner, S. B. (1993). Propagation of ***prions*** with artificial properties in transgenic mice expressing chimeric PrP genes. Cell 73:979-988. NotI fragments, recovered from large-scale DNA cosmid preparations,. . . Walchli, M., Growth, D., Carlson, G., DeArmond, S. J., Westaway, D., and Prusiner, S. B. (1989). Transgenic mice expressing hamster ***prion*** protein produce species-specific infectivity and amyloid plaques. Cell 59:847-857. Genomic DNA isolated from tail tissue of weaning animals was screened. . .

DETD . . . calcium and magnesium ions. For immunoblot analysis, samples were cleared of cell debris by a brief low-speed centrifugation. Purified Hu ***prions*** were prepared using a protocol previously developed for SHa ***prions*** Prusiner et al., (1983) Scrapie ***Prions*** Aggregate to Form Amyloid-like Birefringent Rods. Cell 35, 349-358.

DETD ***Prion*** Inocula

DETD Human brain specimens were collected from patients dying of sporadic, inherited or infectious ***prion*** disease. The iatrogenic CJD denoted 364 was provided by Dr. John Collinge. The RML isolate from Swiss mice Chandler, R.. . .

DETD . . . of inocula and criteria for diagnosis of scrapie in mice have been described Carlson, G. A., et al., "Linage of ***prion*** protein and scrapie incubation time genes," Cell 46:503-511 (1986). When clinical signs of CNS dysfunction appeared, the mice were examined. . .

DETD . . . proteinase K for 60 min at 37.degree. C. Western blots were performed as described previously Barry, R. A., et al., " ***Monoclonal*** antibodies to the cellular and scrapie ***prion*** proteins," J. Infect. Dis., 154:518-521 (1986); Towbin, H., et al., "Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: Procedure. . .

DETD . . . in 1.3 mM HCl and autoclaved at 121.degree. C. for 10 min Muramoto et al., (1992) The sequential development of ***abnormal*** ***prion*** protein accumulation in mice with Creutzfeldt-Jakob disease. Am. J. Pathol. 140, 1411-1420. When temperature decreased, the slides were placed under. . .

DETD Since the Hu ***prion*** inocula are brain homogenates or purified ***prion*** rods from a variety of patients who died of ***prion*** disease, the designations for the patients as well as clinical phenotypes are listed in Table 4 below. The PrP genotypes. . .

DETD TABLE 4

Brain Inocula From Patients Who Died of ***Prion*** Disease

Sporadic Inocula and Infectious CJD ***prions***

Containing wt PrP.sup.Sc

Human Inoculum

Prion Disease

Genotype of PrP.sup.d

PG	sporadic CJD
	wt, M/M129
EC	sporadic CJD
	wt, M/M129
MA	sporadic CJD
	wt, M/M129
PO	sporadic CJD
	wt, M/M129
PC	sporadic CJD
	wt, M/M129
364	iatrogenic CJD
	wt, M/M129

GSS and Familial CJD ***prions*** containing mutant PrP.sup.Sc

JJ GSS P102L, V/V128

LJ-1	familial CJD
	E200K, M/M129
CA	familial CJD
	E200K, M/M129
FH	familial CJD
	E200K, V/M129

.sup.a Substitution. . .

DETD MoPrP.sup.C Inhibits Propagation of Human ***Prions*** in Tg(HuPrP) Mice

DETD When Tg(HuPrP)152/FVB mice and non-Tg littermates were inoculated with Hu ***prions*** from sporadic or iatrogenic CJD as well as inherited ***prion*** disease cases, about 10% of each group of mice developed CNS dysfunction (Telling et al., 1994). Some of the ill mice. . . HuPrP.sup.Sc based on Western immunoblots developed with polyclonal .alpha.-PrP antiserum that reacts with both Hu and MoPrP and with .alpha.-PrP ***monoclonal*** antibodies (mAb) that react with Hu but not MoPrP. Those mice that produced HuPrP.sup.Sc demonstrated that HuPrP.sup.Sc could be formed. . .

DETD After Crossing the Tg(HuPrP) 152/FVB Mice onto the Prnp.sup.0/0 Background, They became Susceptible to Hu ***Prions*** (Table 5)

DETD When Tg(HuPrP)152/FVB mice were inoculated with Hu ***prions*** from a case of sporadic CJD, referred to as RG, only one Tg mouse out of a group of 10. . .

DETD TABLE 5

Transmission Of Hu ***Prions*** to Tg(HuPrP)/Prnp.sup.0/0 mice

Incubation Time

mean d .+-. SEM

Recipient Mouse Line

Inoculum.sup.a

(n/no)

(A) Tg(HuPrP)FVB mice

Tg(HuPrP)152/FVB

sCJD(RG) 721 .+-. 0 (1/10).sup.b

Non-Tg. . .

DETD . . . highly enriched for PrP.sup.Sc prepared from the brain of RG (see Section B of Table 5). Using the .alpha.-PrP 3F4 ***monoclonal*** antibody (mAb) Kascsak, R. J., et al., "Mouse polyclonal and ***monoclonal*** antibody to scrapie-associated fibril proteins," J. Virol. 61:3688-3693 (1987), we estimated, by serial dilution and dot immunoblotting of brain homogenates. . .

DETD . . . of PrP are resistant to scrapie," Cell 73:1339-1347 (1993); Prusiner, S. B., et al., "Immunologic and molecular biological studies of ***prion*** proteins in bovine spongiform encephalopathy," J. Infect. Dis. 167:602-613 (1993); Prusiner, S. B., et al., "Transgenic studies implicate interactions between homologous PrP isoforms in scrapie ***prion*** replication," Cell 63:673-686 (1990), we removed MoPrP.sup.C by producing Tg(HuPrP)152/Prnp.sup.0/0 mice. When Tg(HuPrP)152/Prnp.sup.0/0 were inoculated with Hu ***prions***, they developed signs of neurologic dysfunction with incubation times between 260 and 300 d (Table 5 shown in Section B).

DETD TABLE 6

Transmission of Hu ***prions*** to Tg(MHu2MPrP)mice

Incubation Time

Inoculum.sup.a

mean d.+- SEM (n/no)

(A) Tg(MHu2M)/FVB mice inoculated with sporadic or infectious CJD sCJD(RG) 238.+-3. . .

DETD . . . the length of the incubation time. Although the incubation times are similar for Tg(HuPrP)152/Prnp.sup.0/0 and Tg(MHu2M)5378/Prnp.sup.0/0 mice inoculated with Hu ***prions*** (Tables 5 and 6 Section B of each), the Tg(HuPrP)152/Prnp.sup.0/0 express 5-10-fold more of the transgene product than Tg(MHu2M)5378/Prnp.sup.0/0 mice. . . version may be superior to HuPrP in terms of generating mice with the shortest incubation times for bioassays of Hu ***prions***.

DETD Transmission of Chimeric ***Prions***

DETD . . . significantly to the "species barrier" Prusiner, S. B., et al., "Transgenic studies implicate interactions between homologous PrP isoforms in scrapie ***prion*** replication," Cell 63:673-686 (1990); Scott, M., Foster, D., Mirenda, C., Serban D., Coufal, F., Walchli, M., Growth, D., Carlson, G., DeArmond, S. J., Westaway, D., and Prusiner, S. B. (1989). Transgenic mice expressing hamster ***prion*** protein produce species-specific infectivity and amyloid plaques. Cell 59:847-857. Prolongation of incubation times on primary passage of ***prions*** between species is generally seen while second passage in the same species results in a shortening and stabilization of incubation. . . Monograph 2, D. C. Gajdusek, et al., eds. (Washington, D.C.: U.S. Government Printing), pp. 249-257 (1965). Primary passage of Hu ***prions*** from a sporadic CJD case (EC) produced CNS disease in Tg(MHu2M)5378/FVB with an incubation time of 218.+-5 d(+-SEM) (Table 6. . . Brains from ill mice were collected and homogenates inoculated into mice from the same Tg line. Passage of these chimeric ***prions*** in Tg(MHu2M)5378/FVB mice gave incubation times similar to those seen with Hu ***prions*** on the primary passage (Table 7 Section A). This finding shows that these Tg(MHu2M)5378/FVB mice are completely permissive for Hu ***prions***. Passage of chimeric ***prions*** in Tg(MHu2M)5378/Prnp.sup.0/0 mice resulted in a shortening of the incubation time by .about.20% presumably due to the elimination of MoPrP.sup.C; i.e., ablating the endogenous mouse ***prion*** protein gene.

DETD TABLE 7

Serial transmission of chimeric Hu/Mo ***prions***

in Tg(MHu2M) mice

	Incubation
	Times
	mean d .+-. SEM
Recipient Mouse	(n/no)
Line	Inoculum.sup.a
	Illness Death

(A) Chimeric ***prions*** produced in Tg(MHu2M) mice inoculated with CJD ***prions***

Tg(MHu2M)5378/FVB
MHu2M(sCJD).sup.b
220 .+-. 3 (7/7).sup.c
226 .+-. 1(5)

Non-Tg5378/FVB
MHu2M(sCJD).sup.b
>340

Tg(MHu2M)5378/FVB
MHu2M(sCJD).sup.d
226 .+-. 3 (9/9)
228 .+-. 1(6)

Non-Tg5378/FVB
MHu2M(sCJD).sup.d
>340

Tg(MHu2M)5378/
MHu2M(sCJD).sup.d
189 .+-. 4 (8/8)
192 .+-. 1(4)

Prnp.sup.0/0
Tg(MHu2M)5378/
MHu2M(sCJD).sup.d
183 .+-. 5 (7/7)
190 .+-. 3(4)

Prnp.sup.0/0
(B) Mouse ***prions*** produced in Tg(MHu2M) or non-Tg mice inoculated with RML ***prions***

Tg(MHu2M)5378/FVB
Mo(RML) 178 .+-. 3 (19/19)
203 .+-. 2
(14).sup.e

NonTg5378/FVB
Mo(RML) 127 .+-. 2 (18/18)
156 .+-. 2(5)

Tg(MHu2M)5378/FVB
MHu2M(RML).sup.f
185 .+-. . . >300

Prnp.sup.0/0

.sup.a Notation in parentheses indicate inoculum used in initial passage in Tg(MHu2M) mice.

.sup.b Mice were inoculated with chimeric ***prions*** generated in the brain of

a Tg(MHu2M)5378/FVB mouse that had been inoculated with a brain homogenate prepared from patient EC. . . of mice developing CNS illness divided by the number

inoculated are given in parentheses.

.sup.d Mice were inoculated with chimeric ***prions*** generated in the brain of

a second Tg(MHu2M)5378/FVB mouse that had been inoculated with a brain homogenate prepared from patient EC who died of sporadic CJD.

.sup.e Data from (Telling et al. 1994).

.sup.f Mice were inoculated with Mo ***prions*** generated in the brain of
a

Tg(MHu2M)5378/FVB mouse that had been inoculated with RML Mo ***prions*** .

.sup.g Mice were inoculated with Mo ***prions*** generated in the brain of
a

second Tg(MHu2M)5378/FVB mouse that had been inoculated with RML Mo
prions .

DETD Specificity of Chimeric ***Prions*** and Transgenes

DETD Non-Tg5378/FVB littermates, which express only MoPrP.sup.C, inoculated with the chimeric ***prions*** have remained well for >340 days.

Thus it appears that homology between the substrate PrP.sup.C and the product PrP.sup.Sc in the region bounded by residues 96 to 167 is essential for ***prion*** propagation. Conversely,

Tg(MHu2M)Prnp.sup.0/0 mice are resistant to Mo ***prions*** ; they have remained well for >340 days after inoculation (Table 7 Section B).

DETD Although Tg(MHu2M)5378/FVB mice are permissive for Mo(RML) ***prions*** , the incubation time of 178 ± 3 d (\pm SEM) was protracted compared to that of 127 ± 2 d (\pm SEM) for non-Tg5378/FVB littermates (Table 7 Section B). Two homogenates derived from Tg(MHu2M)5378/FVB mice were inoculated with Mo(RML) ***prions*** were passaged in Tg(MHu2M)5378/FVB mice and non-Tg littermates. The incubation time in the Tg(MHu2M)5378/FVB mice did not change while the incubation time in the non-Tg mice shortened to the incubation time registered for primary passage of Mo(RML) ***prions*** in these mice (Table 7 Section B). This behavior and the fact that MoPrP.sup.Sc is made in response to inoculation with Mo ***prions*** (Telling et al., 1994) appears to show that Tg(MHu2M)5378/FVB mice propagate Mo ***prions*** from endogenous MoPrP.sup.C and not from MHu2MPrP.sup.C.

DETD In Caucasians (Palmer et al., 1991) but not Asians Tateishi and Kitamoto, (1993) Developments in diagnosis for ***prion*** diseases. Br. Med. Bull. 49,971-979 homozygosity for M or V codon 129 has been reported to predispose people to development of sporadic CJD. Homozygosity at codon 129 in some Baker et al., (1991) Amino acid polymorphism in human ***prion*** protein and age at death in inherited ***prion*** disease. Lancet 337, 1286; Goldfarb, L. G., et al., "The molecular genetics of human transmissible spongiform encephalopathy", ***Prion*** Diseases of Humans and Animals, S. B. Prusiner et al., eds. (London: Ellis Horwood), pp. 139-153 (1992) but not other inherited ***prion*** diseases diminished the age of onset of CNS dysfunction; Gabizon et al., (1993) Mutation and polymorphism of the ***prion*** protein gene in Libyan Jews with Creutzfeldt-Jakob disease. Am. J. Hum. Genet 33, 828-835. The Tg(HuPrP)152 mice express HuPrP with . . . codon 129 while another line Tg(HyPrP)440 synthesizes HuPrP with M at 129. When Tg(HuPrP)152/Prnp.sup.0/0 and Tg(HuPrP)440/Prnp.sup.0/0 mice were inoculated with ***prions*** from iatrogenic and sporadic cases, the shortest incubation times occurred when the amino acid residues at position 129 were the . . .

DETD The successful transmission of Hu ***prions*** to Tg(MHu2M)5378/FVB mice promoted us to produce Tg(MHu2M-P101L)69/Prnp.sup.0/0 mice. Unlike the Tg(HuPrP-P102L) mice, these Tg(MHu2M-P101L) mice spontaneously developed neurologic disease.. . .

DETD Transmission of GSS Human ***Prions*** to Tg(MHu2M-P101L) Mice

DETD . . . attempted to determine whether the illness would appear more rapidly if the animals are inoculated. Both wt and GSS Hu ***prions*** were inoculated. Tg(MHu2M-P101L)69Prnp.sup.0/0 mice were inoculated at about 70 days of age with brain extract from a GSS patient referred. . . mutation, or with brain extracts from two sporadic CJD cases (RG and EC in Table 5). These mice inoculated with ***prions*** from the GSS patient JJ died after 171 ± 2.8 d (\pm SEM). The mean age of 247 ± 3 d (\pm SEM) at which these. . . days earlier than the age at which

uninoculated controls developed signs of CNS dysfunction. Although the Tg(MHu2M-P101) mice inoculated with ***prions*** from the sporadic CJD cases have a mean incubation time of 259. \pm 10 d (\pm SEM) (n/n.sub.o =12/15), these mice were 350. \pm 11. . . the time of death. The age of these mice prevented us from concluding whether they became ill from the inoculated ***prions*** or spontaneously as a result of the MHu2MPrP-P102L mutant protein.

DETD Our findings demonstrate that Hu ***prions*** from the GSS patient carrying the point mutation homologous to that in the transgene caused disease more rapidly than did wt Hu ***prions*** from sporadic cases of CJD. Conversely, the Hu ***prions*** from the GSS patient have failed to produce disease >280 d after inoculation in Tg(MHu2M)5376/Prp.sup.0/0 mice (Table 6 Section C); whereas, Hu ***prions*** containing wt PrP.sup.Sc cause disease in Tg(MHu2M)5378/Prp.sup.0/0 mice at .about.190 d (Table 6 Section B). The onset of illness in. . .

DETD Tg(MHu2M-P101L) mice inoculated with GSS ***prions*** exhibited spongiform degeneration and reactive astrocytic gliosis similar to uninoculated Tg(MHu2M-P101L) mice that developed CNS dysfunction spontaneously. However, the inoculated. . . accumulation was more intense in some gray matter regions such as the hippocampus in the Tg(MHu2M-P101L) mice inoculated with GSS ***prions*** than the uninoculated animals exhibiting spontaneous illness.

DETD . . . DeArmond S. J., and Prusiner, S. B. (1994). Serial transmission in rodents of neurologic disease from transgenic mice expressing mutant ***prion*** protein. Likewise, the brain of the GSS patient JJ from which the inoculum was derived contained relatively little or no. . . J., Poulter, M., Owen, F., Terwilliger, J. D., Westaway, D., Ott, J., and Prusiner, S. B. (1989). Linkage of a ***prion*** protein missense variant to Gerstmann-Straussler syndrome. Nature 338:342-345. On some occasions, a weak, diffuse band comigrating with PrP 27-30 has. . . of CNS dysfunction. The relatively short incubation times in the Tg(MHu2M-P101L)69/Prp.sup.0/0 mice argue that the brain of JJ contained high ***prion*** titers even if PrP 27-30 was difficult to detect. From these results, we conclude that PrP.sup.Sc containing the P102L mutation. . .

DETD Transmission of Familial CJD (E200K) Human ***Prions*** to Tg(MHu2M) Mice

DETD . . . (\pm SEM, n=10) for the LJ1 case and .about.160 d for the CA case. In contrast to the P102L mutation, Hu ***prions*** from patients who carried the E200K mutation caused disease as rapidly in Tg(MHu2M)5378/Prp.sup.0/0 mice as Hu ***prions*** containing wtPrP.sup.Sc from sporadic CJD cases (Table 6 Section C).

DETD Transgenic mice expressing moderate to high levels of wild-type human ***prion*** (HuPrP) were originally constructed by microinjecting fertilized FVB embryos with cosmid DNA expressing human PrP. The results of a large number of transmission experiments with sporadic, iatrogenic and familial ***prion*** cases revealed that these mice were no more responsive to human ***prions*** than their non-transgenic counterparts. We have demonstrated that by eliminating endogenous mouse (Mo)PrP expression in these transgenic mice, transmission of human ***prions*** becomes efficient with mean incubation times as low as 160 days. Expression of even half the normal amount of mouse PrP was sufficient to inhibit human ***prion*** propagation. These results demonstrate that Mo PrP is extremely inhibitory for the propagation of human ***prions*** in transgenic mice even though the level of expression of HuPrP was approximately 8 to 16-fold higher than Mo PrP.. . experiments have led to the notion that a third component, which we refer to as protein X, must feature in ***prion*** propagation. Evidence points to the C-terminal region of PrP as the location for the protein X binding site.

DETD The results of these experiments demonstrate that current transgenic mouse models for the assay of human ***prions*** can be improved upon substantially. Because of the inhibitory effects of MoPrP in mice expressing heterologous transgenes, eliminating its expression. . . is crucial for the efficient propagation of heterologous transgenes, eliminating its expressing is crucial for the efficient propagation of heterologous ***prions*** in these transgenic mice. This can be achieved in one of several ways.

DETD . . . in which the sequence for this binding site is mutated. Such a benign MoPrP molecule will not interfere with human ***prion*** propagation in transgenic mice expressing HuPrP because protein X is not sequestered by the mutant MoPrP. Following the above-described procedures. . .

DETD Further modifications of the current transgenic mouse models for the assay of human ***prions*** involve the production of transgenic mice expressing HuPrP under the control of promoter/enhancer sequences from genes other than PrP which. . . will result in levels of expression much higher than normally achieved by PrP promoter/enhancer sequences leading to greatly shortened human ***prion*** incubation times in transgenic mice expressing these constructs. Alternatively, by creating several lines of transgenic mice in which HuPrP expression. .

DETD Mice Expressing Multiple PrP Different Transgenes to Increase the Range of ***Prions*** to which they are Susceptible

DETD . . . from patients with polymorphisms and/or with mutations at particular amino acid residues of HuPrP. We have recently discovered that human ***prion*** propagation, at least in the case of the polymorphism at codon 129 and the GSS mutation at codon 102, occurs. . PrP.sup.C encoded by the transgene. By creating a line in which a number of different forms of HuPrP are expressed, ***prions*** with a variety of different polymorphisms and/or mutations are transmitted efficiently to the same host.

DETD TABLE 8

Prion incubation times in Tg(MoPrP-A) mice	
Incubation Times	
mean d .+-. SEM	
(n/no)	
Recipient Mouse	
Inoculum.sup.a	
Illness.sup.b	
Death.sup.c	

(A) Tg(PrP-A) mice

Tg(MoPrP-A)4053

None 710. . .

CLM What is claimed is:

1. A method of making a standardized ***prion*** preparation, comprising: producing a plurality of transgenic mice each having an ablated endogenous PrP gene and an exogenous PrP gene wherein the mice are susceptible to infection with a ***prion*** which generally only infects a genetically diverse mammal, and further wherein the mice exhibit symptoms of ***prion*** disease within 200 days or less after inoculation with a ***prion*** which generally only infects a genetically diverse mammal; inoculating the mice with a composition comprising ***prions*** from a genetically diverse mammal; observing the mice until the mice exhibit symptoms of ***prion*** infection; harvesting brain tissue from the mice exhibiting symptoms of ***prion*** infection; and homogenizing the harvested brain tissue from said plurality of mice to provide a standardized ***prion***

preparation.

L12 ANSWER 22 OF 23 USPATFULL on STN

AN 1998:95670 USPATFULL

TI Detecting ***prions*** in a sample and ***prion*** preparation and transgenic animal used for same

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RLI Continuation-in-part of Ser. No. US 1995-521992, filed on 31 Aug 1995 which is a continuation-in-part of Ser. No. US 1995-509261, filed on 31 Jul 1995 which is a continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994, now patented, Pat. No. US 5565186

DT Utility

FS Granted

EXNAM Primary Examiner: Stanton, Brian R.

LREP Bozicevic & Reed LLP, Bozicevic, Karl

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 5 Drawing Figure(s); 4 Drawing Page(s)

LN.CNT 3351

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention includes an artificial PrP gene, a transgenic animal containing a PrP gene of another animal or the artificial PrP gene, a hybrid non-human mammal with an ablated endogenous ***prion*** protein gene and exogenous ***prion*** protein gene, assay methodology which uses the animals to detect pathogenic ***prions*** in a sample and standardized ***prion*** preparation used in the assay. The genome of a host animal (such as a mouse), is manipulated so that the animal is rendered susceptible to infection with ***prions*** which normally would infect only a genetically diverse test animal (such as human, cow or sheep). A PrP gene of the host is preferably manipulated to include a mutation which matches a mutation which causes ***prion*** disease in the genetically diverse mammal. Pathogenic ***prions*** in a sample can be detected by injecting the sample to be tested into a mammal of the invention which has been genetically manipulated so as to be susceptible to infection from ***prions*** in the sample. Mammals which are not inoculated with the sample and others inoculated with a standardized ***prion*** preparation of the invention are used as controls in the assay to detect ***prions*** in samples which cause diseases. For example, Creutzfeldt Jakob Disease (CJD) is a fatal neurodegenerative disease of humans caused by ***prions***.

TI Detecting ***prions*** in a sample and ***prion*** preparation and transgenic animal used for same

AB . . . containing a PrP gene of another animal or the artificial PrP gene, a hybrid non-human mammal with an ablated endogenous ***prion*** protein gene and exogenous ***prion*** protein gene, assay methodology which uses the animals to detect pathogenic ***prions*** in a sample and standardized ***prion*** preparation used in the assay. The genome of a host animal (such as a mouse), is manipulated so that the animal is rendered susceptible to infection with ***prions*** which normally would infect only a genetically diverse test animal (such as human, cow or sheep). A PrP gene of the host is preferably manipulated to include a mutation which matches a mutation which causes ***prion*** disease in the genetically diverse mammal. Pathogenic

prions in a sample can be detected by injecting the sample to be tested into a mammal of the invention which has been genetically manipulated so as to be susceptible to infection from ***prions*** in the sample. Mammals which are not inoculated with the sample and others inoculated with a standardized ***prion*** preparation of the invention are used as controls in the assay to detect ***prions*** in samples which cause diseases. For example, Creutzfeldt Jakob Disease (CJD) is a fatal neurodegenerative disease of humans caused by ***prions***.

SUMM . . . animals used in such assays. More specifically, this invention relates to artificial and chimeric PrP genes, assaying samples for pathogenic ***prions***, standardized ***prion*** preparations used in such assays and to transgenic mice and hybrid transgenic mice which can be infected which ***prions*** which generally only infect a genetically diverse species.

SUMM ***Prions*** are infectious pathogens that cause central nervous system spongiform encephalopathies in humans and animals. ***Prions*** are distinct from bacteria, viruses and viroids. The predominant hypothesis at present is that 94 no nucleic acid component is necessary for infectivity of ***prion*** protein. Further, a ***prion*** which infects one species of animal (e.g., a human) will not infect another (e.g., a mouse).

SUMM A major step in the study of ***prions*** and the diseases that they cause was the discovery and purification of a protein designated ***prion*** protein ("PrP") [Bolton et al., Science 218:1309-11 (1982); Prusiner et al., Biochemistry 21:6942-50 (1982); McKinley et al., Cell 35:57-62 (1983)]. Complete ***prion*** protein-encoding genes have since been cloned, sequenced and expressed in transgenic animals. PrPc is encoded by a single-copy host gene. . . et al., Cell 46:417-28 (1986)] and is normally found at the outer surface of neurons. A leading hypothesis is that ***prion*** diseases result from conversion of PrP.sup.C into a modified form called PrP.sup.Sc. However, the actual biological or physiological function of. . .

SUMM It appears that the scrapie isoform of the ***prion*** protein (PrP.sup.Sc) is necessary for both the transmission and pathogenesis of the transmissible neurodegenerative diseases of animals and humans. See Prusiner, S. B., "Molecular biology of ***prion*** disease," Science 252:1515-1522 (1991). The most common ***prion*** diseases of animals are scrapie of sheep and goats and bovine spongiform encephalopathy (BSE) of cattle [Wilesmith, J. and Wells, Microbiol. Immunol. 172:21-38 (1991)]. Four ***prion*** diseases of humans have been identified: (1) kuru, (2) Creutzfeldt-Jakob Disease (CJD), (3) Gerstmann-Strassler-Scheinker Disease (GSS), and (4) fatal familial. . . [Gajdusek, D. C., Science 197:943-960 (1977); Medori et al., N. Engl. J. Med. 326:444-449 (1992)]. The presentation of human ***prion*** diseases as sporadic, genetic and infectious illnesses initially posed a conundrum which has been explained by the cellular genetic origin. . .

SUMM . . . While the most reliable transmission data has been said to emanate from studies using non-human primates, some cases of human ***prion*** disease have been transmitted to rodents but apparently with less regularity [Gibbs, Jr. et al., Slow Transmissible Diseases of the. . . Vol. 2, S. B. Prusiner and W. J. Hadlow, eds. (New York: Academic Press), pp. 87-110 (1979); Tateishi et al., ***Prion*** Diseases of Humans and Animals, Prusiner et al., eds. (London: Ellis Horwood), pp. 129-134 (1992)].

SUMM The infrequent transmission of human ***prion*** disease to rodents has been cited as an example of the "species barrier" first described by Pattison in his studies. . . and M. P. Alpers, eds. (Washington, D.C.: U.S. Government Printing), pp. 249-257 (1965)]. In those investigations, the initial passage of ***prions*** from one species

to another was associated with a prolonged incubation time with only a few animals developing illness. Subsequent. . .

SUMM . . . al., Proc. Natl. Acad. Sci. USA 83:6372-6376 (1986)].

Tg(SH_aPrP) mice expressing SH_aPrP had abbreviated incubation times when inoculated with SH_a ***prions***. When similar studies were performed with mice expressing the human, or ovine PrP transgenes, the species barrier was not abrogated,. . . and the incubation times were unacceptably long. Thus, it has not been possible, for example in the case of human ***prions***, to use transgenic animals (such as mice containing a PrP gene of another species) to reliably test a sample to determine if that sample is infected with ***prions***. The seriousness of the health risk resulting from the lack of such a test is exemplified below.

SUMM . . . used, although the seemingly remote possibility has been raised that increased expression of wtPrP.sup.c stimulated by high GHG might induce ***prion*** disease [Lasmezas et al., Biochem. Biophys. Res. Commun. 196:1163-1169 (1993)]. That the GHG prepared from pituitaries was contaminated with ***prions*** is supported by the transmission of ***prion*** disease to a monkey 66 months after inoculation with a suspect lot of GHG [Gibbs, Jr. et al., N. Engl. J. Med. 328:358-359 (1993)]. The long incubation times associated with ***prion*** diseases will not reveal the full extent of iatrogenic CJD for decades in thousands of people treated with GHG worldwide.. . . Lancet 340:24-27 (1992)]. These cases of iatrogenic CJD underscore the need for screening pharmaceuticals that might possibly be contaminated with ***prions***.

SUMM . . . of such, there clearly is a need for a convenient, cost-effective assay for testing sample materials for the presence of ***prions*** which cause CJD. The present invention offers such an assay.

SUMM The invention comprises a standardized ***prion*** preparation, chimeric PrP genes with mutation codons, transgenic mice which can be used in preparing such a standardized preparation and methods of testing samples using the preparation and transgenic mice. In order to produce the standardized ***prion*** preparation it is necessary to produce a group of non-human host mammals which have their genome manipulated with respect to genetic material related to a PrP gene such that the mammals are susceptible to infection with a ***prion*** which generally only infects an animal which is genetically diverse from the host. The transgenic host animals produced are inoculated with a ***prion*** containing composition and the animals are observed until they exhibit symptoms of ***prion*** infection. Brain tissue is harvested from the animals and homogenized to create the standardized ***prion*** preparation. This process can be repeated one more time using homogenized brain tissue of the last inoculated group to inoculate. . . and thereby further standardize the preparation and reduce any irregularities that might be created by the composition of the initial ***prion*** inoculation composition. Different forms of transgenic animals can be used in the production of different preparations and two or more. . . PrP gene of a genetically diverse species or a completely artificial PrP gene. To test samples for the presence of ***prions*** two sets of non-human transgenic mammals are prepared. Both sets of mammals are designed so that they are susceptible to infection by ***prions*** which would normally only infect a genetically diverse species. The first set of animals are inoculated with a standard ***prion*** preparation and the second set is inoculated with the test sample. Both sets are observed and the set of mammals which is inoculated with a standard ***prion*** preparation is used as a control. If the group of animals inoculated with the test sample develop symptoms of ***prion*** infection then the tester can deduce that the sample includes ***prions***. If the

group inoculated with the test sample does not develop symptoms of ***prion*** disease and the group inoculated with the standard ***prion*** preparation does then the absence of ***prions*** in the sample is deduced.

SUMM . . . are the offspring of different transgenic animals with each other or with a transgenic animal that has an ablated endogenous ***prion*** protein gene, a standardized ***prion*** preparation and assay methodology which uses the preparation and genetically altered animals to detect pathogenic ***prions*** in a sample.

SUMM . . . is inserted into the genome of an animal (such as a mouse), the animal is rendered susceptible to infection with ***prions*** which normally would infect only a specific species of genetically diverse animal (such as a human, cow, sheep, pig, chicken,. . . resulting from a cross between two transgenic animals and in particular a cross between a transgenic animal containing the entire ***prion*** protein gene of a genetically diverse animal (e.g., a mouse containing a human ***prion*** protein gene) and an animal with its endogenous ***prion*** protein gene disrupted (e.g., a mouse with an ablated ***prion*** protein gene). Hybrids also specifically include crossing a transgenic animal having a chimeric ***prion*** protein gene with an animal with its endogenous ***prion*** protein gene ablated.

SUMM . . . the invention are used to create animals which due to their genetic make up will develop disease from inoculation with ***prions*** which would generally only infect a genetically diverse animal, e.g., a mouse of the invention will consistently become infected with ***prions*** which generally will only infect a human and symptoms of the infection will become apparent in a short period e.g.,. . . of the invention are used in assays to test samples of any given material to determine if the material includes ***prions*** which would infect another animal (such as a human) if the material were ingested or injected. Standardized ***prion*** preparations of the invention are used to inoculate animals of the invention to create controls when carrying out an assay of the invention. The standardized ***prion*** preparation will always contain ***prions*** which will infect a genetically modified animal of the invention which animal will develop clinical signs of CNS dysfunction within. . .

SUMM . . . PrP gene which gene includes a portion of a gene of the animal (e.g. human) in danger of infection from ***prions*** in the sample. For example, Creutzfeldt Jakob Disease (CJD) is a fatal neurodegenerative disease of humans caused by ***prions***. Preferred transgenic (Tg) mice disclosed herein express a chimeric ***prion*** protein (PrP) in which a segment of mouse (Mo) PrP (SEQ ID NO: 1) was replaced with the corresponding human. . . (SEQ ID NO: 1) by 9 codons between codons 96 and 167. All of the Tg(MHu2MPPrP) mice injected with human ***prions*** developed neurologic disease. More specifically, the transgenic mice of the invention developed the disease .about.200 days after inoculation with brain homogenates from three CJD patients. When inoculated with CJD ***prions***, MHu2MPPrP.sup.Sc was formed; in contrast MoPrP.sup.Sc was produced if Mo ***prions*** were inoculated. Tg(MHu2MPPrP) mice disclosed herein are useful in the diagnosis, prevention and treatment of human ***prion*** diseases. Transgenic mice containing the artificial PrP gene or elevated levels of expression of a native PrP gene from a genetically diverse animal can be used to test samples for ***prions*** which might infect such animals. The transgenic and hybrid animals disclosed herein consistently develop the adverse effects of such ***prions*** in a relatively short time and are substantially cheaper and easier to maintain than are currently used primate models. Transgenic mice containing a human ***prion*** protein gene are designated Tg(HuPrP) and may be crossed with mice with an ablated endogenous ***prion*** protein gene which are designated Pmp.sup.0/0 to obtain a hybrid designated Tg

(HuPrP)/Pmp.sup.0/0.

SUMM An important object of the invention is to provide a standardized ***prion*** preparation which is produced by inoculating a non-human host animal which has its genome manipulated with respect to its PrP gene so that it is susceptible to infection with ***prions*** which generally only infect an animal genetically diverse from the host animal. The host animal is inoculated with ***prions*** and the animal observed until symptoms of infection occur after which brain tissue is harvested from the animal and homogenized to produce the standardized ***prion*** preparation.

SUMM Yet another object of the invention is to provide for a method of testing samples for the presence of ***prions***. The method involves creating two groups of non-human mammals which have their genome altered so that they are susceptible to infection with ***prions*** which generally only infect a genetically diverse animal. The first group of animals is infected with a test sample and the second group is infected with a standardized ***prion*** preparation. Both groups of mammals are observed in the presence of ***prions*** and the sample can be deduced if the first group of animals develop symptoms of ***prion*** infection.

SUMM An advantage of the invention is that a standardized ***prion*** preparation can be used to provide a control group when testing samples for the presence of ***prions***.

SUMM Another object is to provide a hybrid animal which is obtained by crossing an animal having an ablated endogenous ***prion*** protein gene with a transgenic animal containing (1) a chimeric gene or (2) the ***prion*** protein gene of a genetically diverse animal which gene may be present at elevated levels.

SUMM Another object is to provide a standardized ***prion*** preparation produced from harvested brain tissue taken from animals of the invention (that have substantially identical genomes and specifically have substantially identical genetic material related to ***prions***) which animals exhibit symptoms of ***prion*** infection after being inoculated with ***prions*** which generally only infect a genetically diverse species.

SUMM A feature of the invention is that the standardized ***prion*** preparations of the invention can be used to consistently inoculate control animals with a known amount and type of ***prion***.

SUMM . . . (e.g. a human, cow or sheep) in a manner so as to render the host animal susceptible to infection with ***prions*** which normally infect only the genetically diverse test animal.

SUMM . . . to the PrP gene of the genetically diverse animal which transgenic animal may be used by itself to assay for ***prions*** or for cross-breeding with an animal which has an ablated endogenous ***prion*** protein gene.

SUMM . . . of the present invention is that the transgenic and hybrid animal can be used to assay for the presence of ***prions*** in a sample in a manner which is substantially faster, more efficient and cheaper than presently available assay methods.

SUMM Another advantage is that transgenic and hybrid animals inoculated with ***prions*** of humans can be used as test animals for testing drugs for efficacy in the treatment of humans suffering from diseases resulting from infection with ***prions***.

SUMM Another advantage is that the transgenic and hybrid animals can detect ***prions*** in a sample at very low levels, e.g., 1 part per million, and even as low as 1 part per . . .

SUMM . . . animals provide an assay which is highly accurate, i.e., does not provide false positives and consistently determines the presence of ***prions***.

SUMM Yet another advantage is that by increasing the copy number of an exogenous ***prion*** protein gene of the invention in a transgenic

or hybrid and/or disrupting the endogenous gene of, the incubation time for ***prion*** caused disease is decreased.

SUMM Another advantage is that the standardized ***prion*** preparations of the invention can eliminate the need for extracting brain tissue from mammals which may have been infected with different types of ***prions*** and may each have a different genetic make up regarding genetic material related to ***prions***.

SUMM Another advantage is that assays of the invention can be carried out more reliably using the standardized ***prion*** preparations of the invention.

SUMM A feature of the present invention is that the transgenic and hybrid animals injected with a sample containing pathogenic ***prions*** will consistently develop the disease effects of the ***prions*** within a relatively short time, e.g. about 200 days +/- 50 days after injection or less.

DETD Before the present artificial gene, assay methodology, standardized ***prion*** preparations, and transgenic and hybrid animals used in the assay are described, it is to be understood that this invention is not limited to particular assay methods, chimeric and artificial genes, ***prion*** preparation or transgenic and hybrid animals described, as such methods, genes, preparations, and animals may, of course, vary. It is. . .

DETD . . . commonly used in the production of transgenic mice. For purposes of this invention it should be noted that the mouse ***prion*** protein (PrP) gene is intact and mouse PrP is therefore expressed at normal levels.

DETD The term "Iatrogenic CJD" abbreviated as "iCJD" refers to disease resulting from accidental infection of people with human ***prions***. The most noted example of such is the accidental infection of children with human ***prions*** from contaminated preparations of human growth hormone.

DETD . . . refers to a form of CJD which occurs rarely in families and is inevitably caused by mutations of the human ***prion*** protein gene. The disease results from an autosomal dominant disorder. Family members who inherit the mutations succumb to CJD.

DETD The term "Gerstmann-Strassler-Scheinker Disease" abbreviated as "GSS" refers to a form of inherited human ***prion*** disease. The disease occurs from an autosomal dominant disorder. Family members who inherit the mutant gene succumb to GSS.

DETD The term " ***prion*** " shall mean an infectious particle known to cause diseases (spongiform encephalopathies) in humans and animals. The term " ***prion*** " is a contraction of the words "protein" and "infection" and the particles are comprised largely if not exclusively of PrP^{Sc} molecules encoded by a PrP gene. ***Prions*** are distinct from bacteria, viruses and viroids. Known ***prions*** include those which infect animals to cause scrapie, a transmissible, degenerative disease of the nervous system of sheep and goats as well as bovine spongiform encephalopathies (BSE) or mad cow disease and feline spongiform encephalopathies of cats. Four ***prion*** diseases known to affect humans are (1) kuru, (2) Creutzfeldt-Jakob Disease (CJD), (3) Gerstmann-Strassler-Scheinker Disease (GSS), and (4) fatal familial insomnia (FFI). As used herein ***prion*** includes all forms of ***prions*** causing all or any of these diseases or others in any animals used--and in particular in humans and in domesticated. . .

DETD The terms "PrP gene" and " ***prion*** protein gene" are used interchangeably herein to describe genetic material which expresses proteins as shown in FIGS. 2-5 and polymorphisms. . .

DETD The terms "standardized ***prion*** preparation", " ***prion*** preparation", "preparation" and the like are used interchangeably herein to describe a composition containing ***prions*** which composition is obtained from brain tissue of mammals which contain substantially the

same genetic material as relates to PrP proteins, e.g., brain tissue from a set of mammals which exhibit signs of ***prion*** disease which mammals may comprise any of (1) a PrP chimeric transgene; (2) have an ablated endogenous PrP gene; (3). . . with an ablated endogenous PrP gene and a PrP gene from a genetically diverse species. The mammals from which standardized ***prion*** preparations are obtained exhibit clinical signs of CNS dysfunction as a result of inoculation with ***prions*** and/or due to developing the disease due to their genetically modified make up, e.g., high copy number of PrP genes.

DETD . . . refers generally to any gene of any species which encodes any form of a PrP amino acid sequences including any ***prion*** protein. Some commonly known PrP sequences are described in Gabriel et al., Proc. Natl. Acad. Sci. USA 89:9097-9101 (1992) which. . .

DETD . . . when included in the genome of a host animal (e.g., a mouse) will render the mammal susceptible to infection from ***prions*** which naturally only infect a genetically diverse test mammal, e.g., human, bovine or ovine. In general, an artificial gene will. . . codon of a genetically diverse mammal (such as a human). The genetically altered mammal being used to assay samples for ***prions*** which only infect the genetically diverse mammal. Examples of artificial genes are mouse PrP genes encoding the sequence as shown. . . invention can include not only codons of genetically diverse animals but may include codons and codon sequences associated with genetic ***prion*** diseases such as CJD and codons and sequences not associated with any native PrP gene but which, when inserted into an animal render the animal susceptible to infection with ***prions*** which would normally only infect a genetically diverse animal.

DETD The terms "chimeric gene," "chimeric PrP gene", "chimeric ***prion*** protein gene" and the like are used interchangeably herein to mean an artificially constructed gene containing the codons of a. . . will, when inserted into the genome of a mammal of the host species, render the mammal susceptible to infection with ***prions*** which normally infect only mammals of the second species. The preferred chimeric gene disclosed herein is MHu2M which contains the. . .

DETD The term "genetic material related to ***prions*** " is intended to cover any genetic material which effects the ability of an animal to become infected with ***prions*** . Thus, the term encompasses any "PrP gene", "artificial PrP gene", "chimeric PrP gene" or "ablated PrP gene" which terms are. . . herein as well as mutations and modifications of such which effect the ability of an animal to become infected with ***prions*** . Standardized ***prion*** preparations of the invention are produced using animals which all have substantially the same genetic material related to ***prion*** so that all of the animals will become infected with the same type of ***prions*** and will exhibit signs of infection at about the same time.

DETD . . . may be any animal for which one wishes to run an assay test to determine whether a given sample contains ***prions*** with which the test animal would generally be susceptible to infection. For example, the test animal may be a human, cow, sheep, pig, horse, cat, dog or chicken, and one may wish to determine whether a particular sample includes ***prions*** which would normally only infect the test animal. This is done by including PrP gene sequences of the test animal into the host animal and inoculating the host animal with ***prions*** which would normally only infect the test animal.

DETD The terms "ablated ***prion*** protein gene", "disrupted PrP gene", "ablated PrP gene" and the like are used interchangeably herein to mean an endogenous ***prion*** protein gene which has been altered (e.g., add and/or remove nucleotides) in a manner so as to render the gene. .

DETD . . . any offspring of a hybrid including inbred offspring of two

hybrids provided the resulting offspring is susceptible to infection with ***prions*** with normal infect only a genetically diverse species.

DETD The terms "susceptible to infection" and "susceptible to infection by ***prions***" and the like are used interchangeably herein to describe a transgenic or hybrid test animal of the invention which develops a ***prion*** disease if inoculated with ***prions*** which would normally only infect a genetically diverse test animal. The terms are used to describe a transgenic or hybrid. . . as a transgenic mouse Tg(MHu2M) which, without the chimeric PrP gene, would not be susceptible to infection with a human ***prion*** (less than 20% chance of infection) but with the chimeric gene is susceptible to infection with human ***prions*** (80% to 100% chance of infection).

DETD The term "incubation time" shall mean the time from inoculation of an animal with a ***prion*** until the time when the animal first develops detectable symptoms of disease resulting from the infection. A reduced incubation time. . .

DETD HuPrP for a human ***prion*** protein;

DETD MoPrP for a mouse ***prion*** protein;

DETD SHaPrP for a Syrian hamster ***prion*** protein;

DETD PrP.sup.Sc for the scrapie isoform of the ***prion*** protein;

DETD MoPrP.sup.Sc for the scrapie isoform of the mouse ***prion*** protein;

DETD PrP.sup.CJD for the CJD isoform of a PrP gene; Prn-p.sup.0/0 for ablation of both alleles of an endogenous ***prion*** protein gene, e.g., the MoPrP gene;

DETD Tg(HuPrP)/Prnp.sup.0/0 for a hybrid mouse obtained by crossing a mouse with a human ***prion*** protein gene (HuPrP) with a mouse with both alleles of the endogenous ***prion*** protein gene disrupted;

DETD Tg(MHu2M)/Prnp.sup.0/0 for a hybrid mouse obtained by crossing a mouse with a chimeric ***prion*** protein gene (MHu2M) with a mouse with both alleles of the endogenous ***prion*** protein gene disrupted.

DETD . . . into the genome of a host animal (e.g. a mouse or hamster) will render the animal susceptible to infection with ***prions*** which normally infect only a genetically diverse test animal (e.g. a human, cow or sheep), thereby including genes wherein one. . . is replaced with a corresponding portion of a human PrP gene thereby rendering the mouse susceptible to infection with human ***prions***; (4) a transgenic mammal with elevated levels of expression of a PrP gene of a genetically diverse mammal wherein the. . . or an animal with a PrP gene of another genetically diverse animal therein e.g., as per (4) above; (6) standardized ***prion*** preparations which contain the same amount (preferably at the same concentration) and type of ***prions*** in each preparation; (7) a method of determining whether a sample is infected with ***prions*** which method involves inoculating a transgenic or hybrid mammal of the invention with a sample to be tested (and preferably simultaneously inoculating identical test animals with a standardized ***prion*** preparation for use as controls) and observing the mammal(s) for a period of time sufficient to determine if the mammal(s) develop(s) symptoms of a disease normally associated with ***prions***; (8) a method of testing the efficacy of a drug in the treatment of disease developed as a result of infection with ***prions*** comprising administering a drug to be tested to a transgenic or hybrid animal infected with ***prions*** (preferably a standardized ***prion*** preparation) and observing and/or testing the mammal to determine if the drug aids in treating or slowing the progress of. . . as extracted brain tissue from the animal which has died (and preferably inoculating control animals with a standardized preparation of ***prions***) and observing the transgenic or hybrid animal (and control animals) in order to determine if the animal(s) develop(s) symptoms of ***prion*** infections.

DETD . . . of the invention is to use the animal to test a sample of material to determine if that material has ***prions*** which will infect a human and cause a human to develop a CNS disease such as CJD.

DETD . . . some instances. More specifically, due to small differences in the protein encoded by the PrP gene of different mammals, a ***prion*** which will infect one mammal (e.g. a human) will not normally infect a different mammal (e.g. a mouse). Due to . . . it is not generally possible to use normal animals, (i.e., animal which have not had their genetic material related to ***prions*** manipulated) such as mice to determine whether a particular sample contains ***prions*** which would normally infect a different species of animal such as a human. The present invention solves this problem in. . .

DETD . . . order for the transgenic animals to be useful, it is necessary for the animals to be susceptible to infection with ***prions*** which normally infect only genetically diverse test animals, and in particular animals of commercial significance for testing, such as humans,. . .

DETD . . . the resulting transgenic animal (with a low copy number of human PrP genes) is not susceptible to infection with human ***prions*** .

DETD . . . codons differing between the host and the test animal are switched, the resulting transgenic animal is susceptible to infection with ***prions*** which normally only infect the test animal.

DETD Fifth, we noted that humans with some genetic defects resulting in ***prion*** diseases have different genetic defects in their PrP gene and that by matching the defects in any transgenic animal will render that animal more susceptible to infection with ***prions*** from the diseased human.

DETD . . . with the PrP gene of a test animal to obtain a useful transgenic animal which is susceptible to infection with ***prions*** which normally only infect the test animal by substantially increasing the copy number of the test animal's PrP gene in. . . (SEQ ID NO:2) in a relatively low copy number (e.g. 1 to 4) is not susceptible to infection with human ***prions*** (unless the endogenous mouse PrP gene is ablated). However, if the transgenic mouse includes a very high copy number of. . . a human gene (SEQ ID NO: 2) (e.g. 30-300 copies), the resulting transgenic animal is susceptible to infection with human ***prions*** . Further, when a host animal such as a mouse has only a portion of its PrP gene replaced with a. . . corresponding portion of a test animal such as a human, the resulting transgenic animal is highly susceptible to infection with ***prions*** which normally infect only the test animal. This is true even if the chimeric gene is present in the transgenic. . .

DETD . . . the copy number is not increased so far that the animal becomes spontaneously ill, i.e., become ill without inoculation with ***prions*** .

DETD . . . animal such as a human most preferable where that human PrP gene has a genetic defect which results in a ***prion*** disease when in a human.

DETD . . . the copy number tends to decrease the incubation time for the disease once the animal is inoculated with material containing ***prions*** . Notwithstanding such, we now understand that, when the copy number is increased to very high numbers (e.g. 100 copies and above), the transgenic animals may spontaneously demonstrate symptoms of ***prion*** disease. Thus, a most preferred transgenic animal of the invention will include a chimeric PrP gene in a sufficiently high. . . incubation time (e.g. 50 copies.+-.25) but in a sufficiently low number so as to not initiate spontaneous symptoms characteristic of ***prion*** diseases (e.g., not more than 100 copies). It will be understood by those skilled in the art that the number. . . adjustments can be made to increase the copy number if the resulting

transgenic animals are not subject to infection with ***prions*** which normally infect only a genetically diverse animal. Further, adjustments can be made with respect to the use of specific. . .

DETD . . . the entire PrP gene sequence of the test animal into the host animal and render the host animal susceptible to ***prions*** which normally only infect the test animal even with the host animals endogenous PrP intact i.e., not ablated. However, such. . . that of a human (SEQ ID NO: 2), the resulting transgenic mouse will not be susceptible to infection with human ***prions*** unless (1) the endogenous PrP gene of the mouse is ablated or (2) the human gene is present in the. . . result in spontaneous development of disease and/or (3) the human PrP gene includes a genetic defect which results in a ***prion*** disease in a human.

DETD . . . that the animal would not spontaneously become sick, and yet allow the animal to become sick when inoculated with human ***prions***, we created a chimeric gene which includes only a portion of the human PrP gene in the mouse PrP gene.. . .

DETD When transgenic animals (with endogenous PrP gene intact) are produced by placing the entire human ***prion*** protein gene into that of a mouse the resulting transgenic mouse does not become consistently ill in a short period of time when inoculated with ***prions*** which generally only infect humans i.e., is not susceptible to infection with human ***prions***. The inability to become infected appears to be related to the presence of the endogenous mouse ***prion*** protein gene. When a mouse with a human ***prion*** protein gene is crossed with a mouse with a disrupted endogenous mouse PrP gene the hybrid offspring are infected by ***prions*** which normally only infect humans. Such hybrid mice will consistently become infected and exhibit an incubation time of less than. . .

DETD . . . with a long incubation time. While the high cost of caring for nonhuman primates prevented extensive studies of the human ***prion*** diseases, the transmissibility of these diseases stimulated studies of the animal ***prion*** analogues in rodents [Manuelidis et al., Proc. Natl. Acad. Sci. USA 75:3422-3436 (1978); Manuelidis et al., Proc. Natl. Acad. Sci.. . .

DETD The present disclosure opens a new frontier in the investigation of the human ***prion*** diseases since transmission studies can now be performed relatively rapidly in genetically altered mammals such as Tg(MHu2M) mice that are relatively inexpensive to maintain. For the first time, endpoint titrations of ***prions*** in multiple human body tissues and fluids can be performed and standard curves constructed for more economical incubation time assays. The information derived from such studies of human ***prions*** will be useful in the management of CJD patients who are thought to pose some risk to relatives, physicians, nurses. . .

DETD In studies of human ***prion*** diseases with apes and monkeys, the use of one or two, or rarely three, animals as recipients for a single. . . significant problem in evaluating the transmissibility of a particular inoculum from an individual patient. The transgenic mice contain a chimeric ***prion*** protein gene, e.g., Tg(MHu2M) mice, and hybrid mice e.g., Tg(HuPrP)/Pmp.sup.0/0 described here obviate many of the problems created by using. . .

DETD These results demonstrate the "universality" of the MHu2M transgene for transmission studies with other types of transgenic animals and other ***prion*** inocula. For example, it may be most efficient to use mice expressing MHu2MPrP transgenes coding for either a methionine or. . .

DETD . . . homozygous Met/Met or Val/Val or heterozygous Met/Val at codon 129. The codon 129 polymorphism influences the susceptibility of humans to ***prion*** disease and specifically to iatrogenic and sporadic CJD. This polymorphic codon is contained in the central region of MHu2MPrP which. . .

DETD . . . PrP gene which, when inserted into a host mammal (such as a mouse) renders that mammal susceptible to infection with ***prions*** which normally infect only a genetically diverse test mammal (e.g. a human, cow or sheep). The artificial PrP gene may. . .

DETD . . . segments of the human PrP gene and obtain a transgenic mouse which is subject to being readily infected with human ***prions***. Thus, the invention is not limited to the particular chimeric gene MHu2M or chimeric mice produced using this gene. The. . . types of transgenic animals which include artificial genes wherein the artificial gene renders the transgenic animal susceptible to infection with ***prions*** which normally infect only a genetically diverse animal.

DETD . . . break the "species barrier" by creating a particular chimeric gene whereby transgenic mice can test for the presence of human ***prions*** we have opened the door for the creation of other transgenic animals which will include other artificial PrP genes which, for example, can allow for the testing for the presence of bovine or ovine ***prions*** in a sample. The chimeric or artificial PrP genes can be used by themselves or in an animal with an. . .

DETD Hybrid animals of the invention can be produced by crossing an animal with an ablated endogenous ***prion*** protein gene with either of the transgenic animals mentioned above. For example, a mouse containing a human/mouse chimeric ***prion*** is crossed with a mouse with a disrupted endogenous ***prion*** protein gene e.g., Tg(Pmp.sup.0/0). Alternatively, a mouse containing a high copy number of human ***prion*** protein genes (e.g., 50.+-.25) is crossed with a mouse with a disrupted endogenous ***prion*** protein gene e.g., Tg(Pmp.sup.0/0) to obtain a hybrid Tg(HuPrP)/Pmp.sup.0/0. A variety of different hybrids can be obtained by crossing an animal with an ablated ***prion*** protein gene (i.e., a null ***prion*** background) with different transgenic animals with different ***prion*** protein genes. When successful hybrids are obtained they can be crossed to produce other animals which for the purpose of the disclosure are also considered hybrids if they are susceptible to infection with ***prions*** which generally only infect a genetically diverse species. A null ***prion*** background means that more than 50% of the endogenous ***prion*** protein genes are disrupted, preferable more than 80%, more preferable more than 90% and most preferable 100% so that no. . .

DETD The incubation time of Tg(MHu2M) mice inoculated with Hu ***prions*** is now about 200 days or less +/-50 days, which can be reduced substantially by increasing the copy number of. . . transgene expression was found to be inversely proportional to the length of the scrapie incubation time after inoculation with SHa ***prions*** [Prusiner et al., Cell 63:673-686 (1990)]. Thus, producing Tg(MHu2M) mice with higher levels of transgene expression is a means of. . .

DETD . . . substitutions in other chimeric Hu/Mo PrP constructs, it is possible to further enhance the susceptibility of Tg mice to Hu ***prions*** as reflected by shortened incubation times. Shortening the incubation time is a worthwhile goal for the facilitation of many future studies in ***prion*** research and for the evaluation of pharmaceuticals, foods, tissues, organs, grafts, cosmetics and other substances--particularly substances which have some portion derived from an animal, such as a human, which animal might be infected with ***prions***.

DETD . . . of a chimeric or artificial PrP gene and the incubation time of disease after inoculation of the transgenic animal with ***prions***. Specific MHu2M mice disclosed herein have only 3 or 4 copies of the MHu2M gene. The number of copies can. . .

DETD . . . with codons of the PrP gene of a sheep or cow. The mouse produced would then be susceptible, respectively, to ***prions*** which infect sheep or cows. However, this general method of creating

chimeric genes and using the genes to create chimeric. . .

DETD . . . mutations and polymorphisms at specific sites. When a mutation occurs the individual with the mutation may develop the symptoms of ***prion*** disease without ingesting infectious ***prions***. Homogenized brain tissue from such individuals can be used to inoculate transgenic animals that will then develop symptoms of ***prion*** disease.

DETD Transgenic mice with chimeric PrP genes inoculated with brain tissue derived from an individual with ***prion*** disease resulting from a mutation per the above mutation table may not cause symptoms or may cause symptoms of ***prion*** disease only after an extended time. The present invention provides a means of resolving this problem. Specifically, the chimeric gene. . . is included with the 102 mutation and a transgenic animal is created the resulting transgenic animal will develop symptoms of ***prion*** disease when inoculate with homogenized brain tissue from a human who had ***prion*** disease as a result of the mutation. In certain instances, when the transgenic mouse does not include the mutation which. . . chimeric genes wherein the human portion of the different genes includes the different mutations the mouse will develop symptoms of ***prion*** disease regardless of the type of ***prions*** the mouse is inoculated with. The same results will be obtained with respect to sheep, cows or other animals. More specifically, by determining the point of mutation in the PrP gene which results in ***prion*** disease (of a cow or sheep) one can include such mutations into the chimeric gene being created. When such a. . . mouse/cow) is included within the transgenic animal the resulting animal will develop symptoms of disease regardless of the type of ***prions*** used to inoculate the animal.

DETD . . . PrP genes have been determined allowing, in each case, the prediction of the complete amino acid sequence of their respective ***prion*** proteins. The normal amino acid sequence which occurs in the vast majority of individuals is referred to as the wild-type. . . either five or six repeats of an eight amino acid motif sequence in the amino terminal region of the mature ***prion*** protein. While none of these polymorphisms are of themselves pathogenic, they appear to influence ***prion*** diseases. Distinct from these normal variations of the wild-type ***prion*** proteins, certain mutations of the human PrP gene which alter either specific amino acid residues of PrP or the number of octarepeats have been identified which segregate with inherited human ***prion*** diseases.

DETD The fundamental event in ***prion*** propagation seems to be the conversion of PrP^{sup.C}, which contains about 43% alpha-helix and is devoid of beta-sheet, into PrP^{sup.Sc} which. . . feature in the formation of PrP^{sup.Sc}. One explanation for the difference in susceptibility of Tg(MHu2M) and Tg(HuPrP) mice to Hu ***prions*** in mice may be that mouse chaperons catalyzing the refolding of PrP^{sup.C} into PrP^{sup.Sc} can recognize MHu2MPrP much more readily. . .

DETD . . . In support of this hypothesis is that rodents also differ from ruminants including sheep and cattle at this site; sheep ***prions*** have failed to transmit neurodegeneration to Tg(ShePrP). In these experiments the transgenic mice expressed the entire sheep PrP (SEQ ID.

DETD In contrast to Tg(MHu2M) mice, the overall transmission rate of Hu ***prion*** inocula from a wide variety of sources was less than 10% in Tg(HuPrP) mice, no different from the rate observed. . . appears to be a relatively infrequent event similar to the rare conversion of MoPrP^{sup.C} to PrP^{sup.Sc} in response to human ***prions***. The low rates of transmission in these mice do not seem to be a consequence of low titers of human ***prion*** titers: two inocula which failed to cause disease in Tg(HuPrP) mice transmitted to 100% of inoculated

Tg(MHu2M) animals.

DETD New Approaches To Investigating Human ***Prion*** Diseases

DETD The remarkable sensitivity of Tg(MHu2M) mice to Hu ***prions***

represents an important advance in neurodegenerative disease research. Based on the present disclosure regarding chimeric Hu/Mo PrP transgenes we conceived of a similar approach to the construction of Tg mice susceptible to BSE and scrapie sheep ***prions***. Such would be useful in detecting ***prion*** diseases in domestic animals. The importance of animal ***prion*** diseases is illustrated by BSE or "mad cow disease" in Great Britain, where >150,000 cattle have died and serious consideration has been given to slaughtering millions of cattle potentially infected with ***prions***. This ***prion*** disease BSE is thought to have originated with cattle consuming meat and bone meal produced from sheep offal containing scrapie ***prions*** [Wilesmith, J. W., Semin. Viro. 2:239-245].

DETD . . . sheep scrapie about the risk factors to humans from BSE.

Whether any of these seven amino acid substitutions render bovine ***prions*** permissive in humans remains to be established. It may be that Tg(MHu2M) mice are susceptible to bovine as well as sheep ***prions***. Of perhaps even greater importance, Tg(MHu2M) mice have immediate application in the testing of pharmaceuticals for human ***prion*** contamination. The Tg(MHu2M) mice described here provide a sensitive, reliable and economical bioassay for detecting the presence of human ***prions***.

DETD Standardized ***Prion*** Preparation

DETD Standardized ***prion*** preparations are produced for use in assays

so as to improve the reliability of the assay. Although the preparation can be obtained from any animal it is preferably obtained from a host animal which has brain material containing ***prions*** of a test animal. For example, a Tg mouse containing a human ***prion*** protein gene can produce human ***prions*** and the brain of such a mouse can be used to create a standardized human ***prion*** preparation. The preparation can be further standardized by repeating the above process. More specifically, per the above process some ***prion*** containing material must be used to inoculate the transgenic mice. The source of that ***prion*** containing material may itself be unpredictable and result in infecting transgenic mice in different ways. Thus, if the transgenic mice are infected with a non-standard material some may develop the symptoms of ***prion*** disease at different rates and some may not develop symptoms at all. If a group of mice which develops symptoms of ***prion*** disease at the same time are sacrificed and their brains extracted and homogenized such will create a relatively standard ***prion*** preparation. This preparation can then be used to inoculate a new group of transgenic animals. This process can be repeated. . . times e.g., 1 to 10 times or until such point as all of the transgenic mice are developing symptoms of ***prion*** disease at approximately the same point in time after inoculation with the standardized preparation. Further details of how to produce. . .

DETD . . . and mutations) would spontaneously develop disease and the brain tissue from each could be combined to make a useful standardized ***prion*** preparation.

DETD Standardized ***prion*** preparations can be produced using any of the modified host mammals of the present invention. For example, standardized ***prion*** preparations could be produced using mice, rats, hamsters, or guinea pigs which are genetically modified per the present invention so that they are susceptible to infection with ***prions*** which ***prions*** would generally only infect genetically diverse species such as a human, cow, sheep or horse and which modified host mammals. . . will develop clinical signs of CNS dysfunction within a period of time of 350 days or less after

inoculation with ***prions***. The most preferred host mammal is a mouse in part because they are inexpensive to use and because a greater.

DETD . . . mouse, the next step is to choose the appropriate type of genetic manipulation to be utilized to produce a standardized ***prion*** formulation. For example, the mice may be mice which are genetically modified by the insertion of a chimeric gene of . . . PrP genes into the genome so as to create mice which are susceptible to infection with a variety of different ***prions***, i.e., which generally infect two or more types of test animals. For example, a mouse could be created which included . . . types of chimeric genes were inserted into the genome of the mouse the mouse would be susceptible to infection with ***prions*** which generally only infect a human, cow and sheep.

DETD . . . is to produce a large number of such mammals which are substantially identical in terms of genetic material related to ***prions***. More specifically, each of the mice produced will include an identical chimeric gene present in the genome in substantially the same copy number. The mice should be sufficiently identical genetically in terms of genetic material related to ***prions*** that 95% or more of the mice will develop clinical signs of CNS dysfunction within 350 days or less after. . .

DETD . . . still more preferably 500 or more of such mice are produced. The next step is to inoculate the mice with ***prions*** which generally only infect a genetically diverse mammal e.g., ***prions*** from a human, sheep, cow or horse. The amounts given to different groups of mammals could be varied. After inoculating the mammals with the ***prions*** the mammals are observed until the mammals exhibit symptoms of ***prion*** infection e.g., clinical signs of CNS dysfunction. After exhibiting the symptoms of ***prion*** infection the brain or at least a portion of the brain tissue of each of the mammals is extracted. The extracted brain tissue is homogenized which provides the standardized ***prion*** preparation.

DETD As an alternative to inoculating the group of transgenic mice with ***prions*** from a genetically diverse animal it is possible to produce mice which spontaneously develop ***prion*** related diseases. This can be done, for example, by including extremely high copy numbers of a human PrP (SEQ ID. . . 100 or more copies, the mouse will spontaneously develop clinical signs of CNS dysfunction and have, within its brain tissue, ***prions*** which are capable of infecting humans. The brains of these animals or portions of the brain tissue of these animals can be extracted and homogenized to produce a standardized ***prion*** preparation.

DETD The standardized ***prion*** preparations of the invention can be used directly or can be diluted and tittered in a manner so as to. . . second set of substantially identical mice are inoculated with a material to be tested i.e., a material which may contain ***prions***. A third group of substantially identical mice are not injected with any material. The three groups are then observed. The. . . is also inaccurate probably because the mice have not been correctly created so as to become ill when inoculated with ***prions*** which generally only infect a genetically diverse mammal. However, if the first group does become ill and the third group. . . be presumed to be accurate. Thus, if the second group does not become ill the test material does not contain ***prions*** and if the second group does become ill the test material does contain ***prions***.

DETD By using standardized ***prion*** preparations of the invention it is possible to create extremely dilute compositions containing the ***prions***. For example, a composition containing one part per million or less or even one part per billion or less can. . . composition can be used to test the sensitivity of the transgenic mice

of the invention in detecting the presence of ***prions*** in the sample.

DETD ***Prion*** preparations of the present invention are desirable in that they will include a constant amount of ***prions*** and are extracted from an isogenic background. Accordingly, contaminants in the preparations will be constant and controllable. Standardized ***prion*** preparations of the invention will be useful in the carrying out of bioassays in order to determine the presence, if any, of ***prions*** in various pharmaceuticals, whole blood, blood fractions, foods, cosmetics, organs and in particular any material which is derived from an animal (living or dead) such as organs, blood and products thereof derived from living or dead humans. Thus, standardized ***prion*** preparations of the invention will be valuable in validating purification protocols where preparations are spiked and reductions in titer measured. . .

DETD Measuring Levels Of ***Prions***

DETD The present invention can be utilized to determine the concentration of ***prions*** (which generally only infect a genetically diverse animal) within a given sample. The transgenic mice make it possible to test for the positive presence of ***prions*** within a sample. The mice are capable of detecting the presence of ***prions*** in a concentration as low as 1 ppm or even 1 ppb or less. The procedure for doing such will. . . to disclose such a method of measurement. In general, the method is carried out by determining the titer of the ***prions*** by carrying out measurements of time intervals from inoculation to onset of symptoms and from inoculation to death. The intervals. . .

DETD Since the fundamental event underlying ***prion*** propagation seems to be a conformational change in PrP [Pan et al., Proc. Natl. Acad. Sci. USA 90:10962-10966 (1993)] and. . . positions out of 254 [Kretzschmar et al., DNA 5:315-324 (1986)], we constructed modified PrP transgenes. Chimeric SHa/Mo transgenes have produced ***prions*** with new properties, the most useful being the chimeric SHa/Mo transgene labeled MH2M which carries 5 amino acid substitutions found. . .

DETD Mice expressing the MHu2M chimeric transgene are susceptible to human ***prions*** after abbreviated incubation times. More specifically, the transgenic mice of the present invention which include the chimeric MHu2M gene will, after inoculation with human ***prions***, develop disease symptoms attributed to the ***prions*** within about 200 days.+-.50 days. Further, 80% or more the transgenic mice of the invention inoculated with human ***prions*** will develop symptoms of the disease, more preferably 98% or more of the mice will develop symptoms of the disease. According to experiments carried out, 100% of the transgenic MHu2M mice inoculated with human ***prions*** actually developed symptoms of the disease in about 200 days or less.+-.50 days.

DETD . . . neurodegeneration more rapidly than monkeys, they provide a preferred host for bioassays of infectivity in tissues of humans dying of ***prion*** diseases. The Tg(MHu2M) mice disclosed herein provide an excellent system for assessing the sterility of pharmaceuticals as well as tissue and organ grafts prepared from human sources. Other transgenic mice which include the ***prion*** protein gene of the animal in danger of infection can be used to test samples for ***prion*** diseases which can infect domestic animals such as sheep and cattle.

DETD . . . PrP genes can be created which, when inserted into a host animal, will render that animal susceptible to infection with ***prions*** which normally only infect a second and genetically diverse test animal. There are nearly an infinite number of possible artificial. . . would meet the basic criteria of the invention, i.e. rendering a mammal such as a mouse susceptible to infection with

prions which normally infect only a genetically diverse test animal such as a human. The MHu2M gene of the invention is. . . are included. Transgenic mice expressing only low levels of human PrP.sup.C are unlikely to become ill after inoculation with human ***prions***. However, if the level of human PrP.sup.C expression is elevated, the transgenic animals become susceptible to infection with human ***prions***. This is another means of overcoming the species barrier by what is referred to as a stochastic process.

DETD . . . the resulting gene could be inserted into a mouse in order to render the mouse susceptible to infection with bovine ***prions***. A similar strategy with respect to producing a mouse which would be susceptible to infection with sheep ***prions*** can be deduced from reviewing FIG. 5. In addition to these possibilities those skilled in the art will recognize that, . . . to obtain a useful artificial gene which, when inserted into an animal, will render that animal susceptible to infection with ***prions*** which normally would infect only a genetically diverse mammal.

DETD . . . mammal will express the PrP gene at a level sufficiently high to render the host animal susceptible to infection with ***prions*** which normally only infect a genetically diverse test animal.

DETD PrP.sup.Sc has been found in the brains of affected Tg(MHu2M) mice after inoculation with Hu(CJD) or Mo(RML) ***prions***. Brain homogenates of Tg(MHu2M) were either left undigested or digested with proteinase K (BMB) at a final concentration of 20. . .

DETD The distribution of PrP.sup.C and PrP.sup.Sc in clinically sick Tg(MHu2M) mice inoculated with Mo(RML) and Hu(CJD) ***prions*** were detected by the histoblot method. The histoblots included those of coronal sections through the region of the hippocampus and. . .

DETD . . . of these offspring. As shown in Example 5 below, these mice were found to be susceptible to infection with human ***prions*** 100% of the time.

DETD Sources of ***Prion*** Inocula

DETD . . . clinical diagnosis of CJD or GSS had been confirmed by histopathological examination of brain tissues and, in most cases, by ***prion*** protein analysis. In some cases, the PrP gene was amplified by PCR of DNA isolated from patient blood and the. . .

DETD . . . to X-ray film for 5-60 seconds. .alpha.-PrP RO73 rabbit antiserum was used at a final dilution of 1:5000 and 3F4 ***monoclonal*** antibody was also employed [Serban et al., Neurology 40:110-117 (1990)].

DETD Tg(MHu2MPrP) Mice Are Susceptible to Human ***Prions***

DETD Inoculation of Tg(MHu2M) mice with Mo(RML) ***prions*** passaged in mice produced disease in 178.+-.3 days, which is .about.40 longer than Mo(RML) ***prions*** in non-Tg mice. Prolongation of incubation times in mice expressing non-murine transgenes is well established, and occurs presumably because the. . . conversion of MoPrP.sup.C into MoPrP.sup.Sc [Prusiner et al., Cell 63:673-686 (1990)]. In contrast to Tg(MHu2M) mice, incubation times for RML ***prions*** in Tg(MH2M) mice were the same as those of the non-Tg mice [Scott et al., Cell 73:979-988 (1993)].

DETD TABLE 1

Incubation of human (CJD) and mouse (RML) ***prion***
inocula in Tg (MHu2M) FVB-B5378 mice
Incubation Times
(mean days .+-. SE)
Range
Source Inoculum No..sup.a
(days) Illness
Death.sup.b

Sporadic

RG 8/8 225-249

238 .+-. . .

DETD Tg(HuPrP) Mice Are Resistant to Human ***Prions***

DETD To determine whether expression of HuPrP (SEQ ID NO:2) in Tg(HuPrP)B6SJL-110 and Tg(HuPrP)FVB-152 conferred susceptibility to human ***prions***, incubation periods were measured after inoculation of Tg(HuPrP) and non-Tg mice with brain extracts from 18 patients that had died. . . 2.5 years, we concluded that the two lines of Tg(HuPrP) mice were no more responsive than non-Tg mice to human ***prions*** (see Table 2 below). The rate of transmission to Tg(HuPrP) mice was 8.3% (14 clinically sick mice out of 169. . . after extremely long incubation periods is compounded by the heightened potential for artifactual results due to low levels of contaminating ***prions***.

DETD Statistical analysis shows that the frequency of Hu ***prion*** transmission to Tg(MHu2MPrP) mice compared to Tg(HuPrP) and non-Tg mice is highly significant using the Fisher's exact test, $p < 10^{-7}$ [Mehta et al., J. Am. Stat. Assn. 78:(392) 427-434 (1983)]. When Hu ***prion*** transmission to Tg(HuPrP) mice was compared to non-Tg mice, the frequencies were similar, $p = 0.79$.

DETD To confirm the clinical diagnosis of ***prion*** disease, 5 ill Tg(HuPrP) and 1 non-Tg mice were sacrificed and brain extracts were examined for the presence of PrP^{sup.Sc}. . . mice which developed clinical signs after 589 days post-inoculation with iatrogenic CJD inoculum #170. The equivalent transmission rates of human ***prions*** in Tg(HuPrP) and non-Tg mice indicate that this is a rare event with the same frequency of occurrence as the stochastic conversion of MoPrP^{sup.C} to MoPrP^{sup.Sc} induced by human ***prions***.

DETD . . . 3F4-reactive PrP^{sup.Sc} in the brains of 3 out of the 6 mice analyzed may reflect the difficulty of accurately diagnosing ***prion*** disease in elderly animals. Some of the mice inherited ***prion*** diseases of both humans and Tg mice exhibit little or undetectable levels of protease-resistant PrP; yet, based on transmission studies, their brains contain ***prions*** and they show clear spongiform degeneration [Medori et al., N. Engl. J. Med. 326:444-449 (1992)].

DETD In contrast to Tg(MHu2M) mice, Hu ***prions*** from patient RG have not transmitted to either Tg(HuPrP) or non-Tg mice after >330 days (see Table 2 below). Attempts to transmit preparations enriched for Hu ***prion*** rods prepared from the brain of patient RG have likewise been negative for >300 days. In addition, inoculum from the. . .

DETD TABLE 2

Incubation times in Tg(HuPrP)FVB-152 and Tg(HuPrP)B6SJL-110 mice after inoculation with brain extracts from patients with human ***prion*** diseases

	Incubation times
Host	Inoculum (n/n.sub.o).sup.a (days .+-. SE).sup.b

Tg 152	Sporadic	1/10	706
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CJD (#87011)

Non-Tg	Sporadic	3/5	697.3 .+-. 51
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CJD. . .

DETD Some clinically sick Tg(MHu2M) mice inoculated with each of the three CJD ***prion*** inocula or RML ***prions*** were sacrificed for histopathological verification of disease and for ***prion*** protein analysis. Western blots of brain homogenates from Tg(MHu2M) mice infected with Hu ***prions*** probed with RO73 and 3F4 .alpha.-PrP

antibodies revealed the presence of protease-resistant PrP^{sup}.Sc which reacted with the 3F4 ***monoclonal*** antibody showing this protease-resistant product to be MHu2M PrP^{sup}.Sc. The epitope recognized by this antibody consists of a pair of . . . with MHu2MPrP^{sup}.Sc as well as HuPrP^{sup}.C and HuPrP^{sup}.Sc from diseased human brains. Brain homogenates from Tg(MHu2M) mice infected with RML ***prions*** contained PrP^{sup}.Sc which was detectable only with RO73 and not 3F4 .alpha.-PrP antibodies, indicating that Tg(MHu2M) mice are capable of producing MoPrP^{sup}.Sc but not MHu2MPrP^{sup}.Sc in response to RML ***prions*** previously passaged in mice. While these findings are similar to those reported for Tg(SHaPrP) mice [Scott et al., Cell 59:847-857 (1989)], they contrast with those found for Tg(MH2MPrP) mice where MH2MPrP^{sup}.Sc was formed in response to RML ***prions*** [Scott et al., Cell 73:979-988 (1993)].

DETD . . . shown in histoblots of coronal brain sections through the hippocampus and thalamus of Tg(MHu2M) mice inoculated with RML or CJD ***prions***. The weak immunoreactivity of MHu2M PrP with RO73 permitted a degree of analysis which had not been previously possible in . . . react with this antibody. The pattern of PrP^{sup}.Sc deposition was highly dependent upon the species of origin of the infectious ***prions***. When inoculated with RML ***prions***, histoblots of the brains of Tg(MHu2M) were similar to those of CD-1 mice infected with RML ***prions***, revealing a diffuse pattern of MoPrP^{sup}.Sc deposition in the hippocampus, thalamus, hypothalamus and all layers of the neocortex. The histoblot pattern of was strikingly different for Tg(MHu2M) mice inoculated with CJD ***prions***. The deposition of MHu2MPrP^{sup}.Sc was confined primarily to the deep layers of the neocortex, the thalamus, particularly the ventral posterior. . . signal. The same pattern of MHu2MPrP^{sup}.Sc deposition was consistently observed in histoblots of Tg(MHu2M) mice inoculated with all three CJD ***prion*** isolates prepared from human brain. It is noteworthy that the pattern of MHu2MPrP^{sup}.Sc deposition is similar to the pattern of . . . Natl. Acad. Sci. USA 89:7620-7624 (1992)]. The spongiform degeneration in the brains of Tg(MHu2M) mice infected with Mo(RML) and Hu(CJD) ***prions*** reflected the patterns of PrP^{sup}.Sc accumulation described above.

DETD . . . methods are listed in Tables 3-7. With respect to such the (1) methods of making mice; (2) brain homogenates; (3) ***prion*** inocula; (4) measurement of incubation times; (5) immunoblotting; and (6) immunohistochemistry are described below.

DETD . . . at codon 102 of the human PrP gene has been described Hsiao, K. and Prusiner, S. B. (1990). Inherited human ***prion*** diseases. Neurology 40:1820-1827. ORF cassettes were digested with BglII (which cleaves immediately adjacent to the initiation codon). The 5' protruding . . . to the SalI-cut cosSHa.Tet cosmid expression vector Scott, M. R., Kohler, R., Foster, D., and Prusiner, S. B. (1992). Chimeric ***prion*** protein expression in cultured cells and transgenic mice. Protein Sci. 1:986-997. The isolation of recombinant cosmid clones was achieved by . . . Scott, M., Groth D., Foster, D., Torchia, M., Yang, S.-L., DeArmond, S. J., and Prusiner, S. B. (1993). Propagation of ***prions*** with artificial properties in transgenic mice expressing chimeric PrP genes. Cell 73:979-988. NotI fragments, recovered from large-scale DNA cosmid preparations, . . . Walchli, M., Growth, D., Carlson, G., DeArmond, S. J., Westaway, D., and Prusiner, S. B. (1989). Transgenic mice expressing hamster ***prion*** protein produce species-specific infectivity and amyloid plaques. Cell 59:847-857. Genomic DNA isolated from tail tissue of weaning animals was screened. . .

DETD . . . calcium and magnesium ions. For immunoblot analysis, samples were cleared of cell debris by a brief low-speed centrifugation. Purified Hu ***prions*** were prepared using a protocol previously

developed for SHa ***prions*** Prusiner et al., (1983) Scrapie
 Prions Aggregate to Form Amyloid-like Birefringent Rods. Cell
 35, 349-358.

DETD ***Prion*** Inocula

DETD Human brain specimens were collected from patients dying of sporadic,
 inherited or infectious ***prion*** disease. The iatrogenic CJD
 denoted 364 was provided by Dr. John Collinge. The RML isolate from
 Swiss mice Chandler, R.. . .

DETD . . . of inocula and criteria for diagnosis of scrapie in mice have
 been described Carlson, G. A., et al., "Linkage of ***prion***
 protein and scrapie incubation time genes," Cell 46:503-511 (1986). When
 clinical signs of CNS dysfunction appeared, the mice were examined. .

DETD . . . proteinase K for 60 min at 37.degree. C. Western blots were
 performed as described previously Barry, R. A., et al., "
 Monoclonal antibodies to the cellular and scrapie ***prion***
 proteins," J. Infect. Dis., 154:518-521 (1986); Towbin, H., et al.,
 "Electrophoretic transfer of proteins from polyacrylamide gels to
 nitrocellulose sheets:. . .

DETD . . . in 1.3 mM HCl and autoclaved at 121.degree. C. for 10 min
 Muramoto et al., (1992) The sequential development of ***abnormal***
 prion protein accumulation in mice with Creutzfeldt-Jakob
 disease. Am. J. Pathol. 140, 1411-1420. When temperature decreased, the
 slides were placed under. . .

DETD Since the Hu ***prion*** inocula are brain homogenates or purified
 prion rods from a variety of patients who died of ***prion***
 disease, the designations for the patients as well as clinical
 phenotypes are listed in Table 4 below. The PrP genotypes. . .

DETD TABLE 4

Brain Inocula From Patients Who Died of ***Prion*** Disease
 Sporadic Inocula and Infectious CJD ***prions***
 Containing wt PrP.sup.5c
 Prion

Human Inoculum

Disease Genotype of PrP.sup.d

PG	sporadic CJD
	wt, M/M129
EC	sporadic CJD
	wt, M/M129
MA	sporadic CJD
	wt, M/M129
PO	sporadic CJD
	wt, M/M129
PC	sporadic CJD
	wt, M/M129
364	iatrogenic CJD
	wt, M/M129

GSS and Familial CJD ***prions*** containing mutant PrP.sup.5c
 JJ GSS P102L, V/V128

LJ-1	familial CJD
	E200K, M/M129
CA	familial CJD
	E200K, M/M129
FH	familial CJD
	E200K, V/M129

.sup.a Substitution. . .

DETD MoPrP.sup.C Inhibits Propagation of Human ***Prions*** in Tg(HuPrP) Mice

DETD When Tg(HuPrP) 152/FVB mice and non-Tg littermates were inoculated with Hu ***prions*** from sporadic or iatrogenic CJD as well as inherited ***prion*** disease cases, about 10% of each group of mice developed CNS dysfunction (Telling et al., 1994). Some of the ill mice. . . .alpha.-PrP antiserum that reacts with both Hu (SEQ ID NO: 2) and MoPrP (SEQ ID NO: 1) and with .alpha.-PrP ***monoclonal*** antibodies (mAb) that react with Hu (SEQ ID NO: 2) but not MoPrP (SEQ ID NO:1). Those mice that produced. . .

DETD After Crossing the Tg(HuPrP) 152/FVB mice onto the Prnp.sup.0/0 background, they became susceptible to Hu ***prions*** (Table 5)

DETD When Tg(HuPrP) 152/FVB mice were inoculated with Hu ***prions*** from a case of sporadic CJD, referred to as RG, only one Tg mouse out of a group of 10. . .

DETD TABLE 5

Transmission Of Hu ***Prions*** to Tg(HuPrP)/Prnp.sup.0/0 mice
Incubation Time
mean d .+-. SEM
Recipient Mouse Line Inoculum.sup.a
(n/no)

(A) Tg(HuPrP)FVB Mice

Tg(HuPrP)152/FVB

sCJD(RG) 721 .+-. 0. . .

DETD . . . highly enriched for PrP.sup.Sc prepared from the brain of RG (see Section B of Table 5). Using the .alpha.-PrP 3F4 ***monoclonal*** antibody (mAb) Kascsak, R. J., et al., "Mouse polyclonal and ***monoclonal*** antibody to scrapie-associated fibril proteins," J. Virol. 61:3688-3693 (1987), we estimated, by serial dilution and dot immunoblotting of brain homogenates. . .

DETD . . . of PrP are resistant to scrapie," Cell 73:1339-1347 (1993); Prusiner, S. B., et al., "Immunologic and molecular biological studies of ***prion*** proteins in bovine spongiform encephalopathy," J. Infect. Dis. 167:602-613 (1993); Prusiner, S. B., et al., "Transgenic studies implicate interactions between homologous PrP isoforms in scrapie ***prion*** replication," Cell 63:673-686 (1990), we removed MoPrP.sup.C by producing Tg(HuPrP) 152/Prnp.sup.0/0 mice. When Tg(HuPrP) 152/Prnp.sup.0/0 were inoculated with Hu ***prions***, they developed signs of neurologic dysfunction with incubation times between 260 and 300 d (Table 5 shown in Section B).

DETD TABLE 6

Transmission of Hu ***prions*** to Tg (MHu2MPPrP) mice
Incubation Time
Inoculum.sup.a mean d .+-. SEM (n/no)

(A) Tg (MHu2M)/FVB mice inoculated with sporadic or infectious CJD sCJD (RG). . .

DETD . . . length of the incubation time. Although the incubation times are similar for Tg(HuPrP) 152/Prnp.sup.0/0 and Tg(MHu2M)5378/Prnp.sup.0/0 mice inoculated with Hu ***prions*** (Tables 5 and 6 Section B of each), the Tg(HuPrP) 152/Prnp.sup.0/0 express 5-10-fold more of the transgene product than Tg(MHu2M)5378/Prnp.sup.0/0. . . version may be superior to HuPrP in terms of generating mice with the shortest incubation times for bioassays of Hu ***prions***.

DETD Transmission Of Chimeric ***Prions***

DETD . . . significantly to the "species barrier" Prusiner, S. B., et al., "Transgenic studies implicate interactions between homologous PrP isoforms in scrapie ***prion*** replication," Cell 63:673-686 (1990); Scott, M., Foster, D., Mirenda, C., Serban D., Coufal, F., Walchli, M., Growth, D., Carlson, G., DeArmond, S. J., Westaway, D., and Prusiner, S. B. (1989). Transgenic mice expressing hamster ***prion*** protein produce species-specific infectivity and amyloid plaques. Cell 59:847-857. Prolongation of incubation times on primary passage of ***prions*** between species is generally seen while second passage in the same species results in a shortening and stabilization of incubation. . . Monograph 2, D. C. Gajdusek, et al., eds. (Washington, D.C.: U.S. Government Printing), pp. 249-257 (1965). Primary passage of Hu ***prions*** from a sporadic CJD case (EC) produced CNS disease in Tg(MHu2M)5378/FVB with an incubation time of 218. \pm .5 d(\pm .SEM) (Table 6. . . Brains from ill mice were collected and homogenates inoculated into mice from the same Tg line. Passage of these chimeric ***prions*** in Tg(MHu2M)5378/FVB mice gave incubation times similar to those seen with Hu ***prions*** on the primary passage (Table 7 Section A). This finding shows that these Tg(MHu2M)5378/FVB mice are completely permissive for Hu ***prions***. Passage of chimeric ***prions*** in Tg(MHu2M)5378/Prnp.sup.0/0 mice resulted in a shortening of the incubation time by .about.20% presumably due to the elimination of MoPrP.sup.C ; i.e., ablating the endogenous mouse ***prion*** protein gene.

DETD TABLE 7

Serial transmission of chimeric Hu/Mo ***prions*** in Tg (MHu2M) mice.

Recipient	Incubation Times mean d \pm SEM (n/no)	Illness	Death
Mouse Line Inoculum.sup.a			

(A) Chimeric ***prions*** produced in Tg (MHu2M) mice inoculated with CJD ***prions***

Tg (MHu2M) MHu2M (sCJD).sup.b	220 \pm 3 (7/7).sup.c
5378/FVB	226 \pm 1 (5)

Non-Tg5378/FVB	
MHu2M (sCJD).sup.b	>340

Tg (MHu2M) MHu2M (sCJD).sup.d	226 \pm 3. . . \pm 4 (8/8)
Prnp.sup.0/0	192 \pm 1 (4)

Tg (MHu2M) 5378/	
MHu2M (scJD).sup.d	183 \pm 5 (7/7)
Prnp.sup.0/0	190 \pm 3 (4)

(B) Mouse ***prions*** produced in Tg (MHu2M) or non-Tg mice inoculated with RML ***prions***

Tg (MHu2M) Mo (RML)	178 \pm 3 203 \pm 2 (14).sup.e
5378/FVB	(19/19)

NonTg5378/FVB	
Mo (RML)	127 \pm 2 156 \pm 2 (5)

. . . .sup.a Notation in parentheses indicate inoculum used in initial passage

in Tg (MHu2M) mice.

.sup.b Mice were inoculated with chimeric ***prions*** generated in the brain of

a Tg (MHu2M) 5378/FVB mouse that had been inoculated with a brain homogenate prepared from . . . of mice developing CNS illness divided by the number

inoculated are given in parentheses.

.sup.d Mice were inoculated with chimeric ***prions*** generated in the brain of

a second Tg (MHu2M) 5378/FVB mouse that had been inoculated with a brain homogenate prepared. . . patient EC who died of sporadic CJD.

.sup.e Data from (Telling et al. 1994).

.sup.f Mice were inoculated with Mo ***prions*** generated in the brain of a Tg

(MHu2M) 5378/FVB mouse that had been inoculated with RML Mo ***prions*** .

.sup.g Mice were inoculated with Mo ***prions*** generated in the brain of a

second Tg (MHu2M) 5378/FVB mouse that had been inoculated with RML Mo ***prions*** .

DETD Specificity Of Chimeric ***Prions*** And Transgenes

DETD Non-Tg5378/FVB littermates, which express only MoPrP.sup.C, inoculated with the chimeric ***prions*** have remained well for >340 days.

Thus it appears that homology between the substrate PrP.sup.C and the product PrP.sup.Sc in the region bounded by residues 96 to 167 is essential for ***prion*** propagation. Conversely,

Tg(MHu2M)Prnp.sup.0/0 mice are resistant to Mo ***prions*** ; they have remained well for >340 days after inoculation (Table 7 Section B).

DETD Although Tg(MHu2M)5378/FVB mice are permissive for Mo(RML)

prions , the incubation time of 178.+-.3 d(+-.SEM) was protracted compared to that of 127.+-.2 d(+-.SEM) for non-Tg5378/FVB littermates (Table 7 Section B). Two homogenates derived from Tg(MHu2M)5378/FVB mice were inoculated with Mo(RML) ***prions*** were passaged in Tg(MHu2M)5378/FVB mice and non-Tg littermates. The incubation time in the Tg(MHu2M)5378/FVB mice did not change while the incubation time in the non-Tg mice shortened to the incubation time registered for primary passage of Mo(RML) ***prions*** in these mice (Table 7 Section B). This behavior and the fact that MoPrP.sup.Sc is made in response to inoculation with Mo ***prions*** (Telling et al., 1994) appears to show that Tg(MHu2M)5378/FVB mice propagate Mo ***prions*** from endogenous MoPrP.sup.C and not from MHu2MPrP.sup.C.

DETD In Caucasians (Palmer et al., 1991) but not Asians Tateishi and Kitamoto, (1993) Developments in diagnosis for ***prion*** diseases.

Br. Med. Bull. 49,971-979 homozygosity for M or V codon 129 has been reported to predispose people to development of sporadic CJD.

Homozygosity at codon 129 in some Baker et al., (1991) Amino acid polymorphism in human ***prion*** protein and age at death in inherited ***prion*** disease. Lancet 337, 1286; Goldfarb, L. G., et al., "The molecular genetics of human transmissible spongiform encephalopathy", ***Prion*** Diseases of Humans and Animals, S. B.

Prusiner et al., eds. (London: Ellis Horwood), pp. 139-153 (1992) but not other inherited ***prion*** diseases diminished the age of onset of CNS dysfunction; Gabizon et al., (1993) Mutation and polymorphism of the ***prion*** protein gene in Libyan Jews with Creutzfeldt-Jakob disease. Am. J. Hum. Genet 33, 828-835 . The Tg(HuPrP) 152 mice express.

. . line Tg(HuPrP)440 synthesizes HuPrP (SEQ ID NO: 2) with M at 129. When Tg(HuPrP)152/Prnp.sup.0/0 and Tg(HuPrP)440/Prnp.sup.0/0 mice were inoculated with ***prions*** from iatrogenic and sporadic cases, the shortest incubation times occurred when the amino acid residues at position 129 were the. . .

DETD The successful transmission of Hu ***prions*** to Tg(MHu2M)5378/FVB mice promoted us to produce Tg(MHu2M-P101L)69/Prnp.sup.0/0 mice. Unlike

the Tg(HuPrP-P102L) mice, these Tg(MHu2M-P101L) mice spontaneously developed neurologic disease.. . .

DETD Transmission Of GSS Human ***Prions*** To Tg(MHu2M-P101L) Mice

DETD . . . attempted to determine whether the illness would appear more rapidly if the animals are inoculated. Both wt and GSS Hu ***prions*** were inoculated. Tg(MHu2M-P101L)69Prnp.sup.0/0 mice were inoculated at about 70 days of age with brain extract from a GSS patient referred. . . mutation, or with brain extracts from two sporadic CJD cases (RG and EC in Table 5). These mice inoculated with ***prions*** from the GSS patient JJ died after 171. \pm 2.8 d (\pm SEM). The mean age of 247. \pm 3 d (\pm SEM) at which these. . . days earlier than the age at which uninoculated controls developed signs of CNS dysfunction. Although the Tg(MHu2M-P101L) mice inoculated with ***prions*** from the sporadic CJD cases have a mean incubation time of 259. \pm 10 d (\pm SEM) (n/n.sub.o =12/15), these mice were 350. \pm 11. . . the time of death. The age of these mice prevented us from concluding whether they became ill from the inoculated ***prions*** or spontaneously as a result of the MHu2MPPrP-P102L mutant protein.

DETD Our findings demonstrate that Hu ***prions*** from the GSS patient carrying the point mutation homologous to that in the transgene caused disease more rapidly than did wt Hu ***prions*** from sporadic cases of CJD. Conversely, the Hu ***prions*** from the GSS patient have failed to produce disease >280 d after inoculation in Tg(MHu2M)5376/Prnp.sup.0/0 mice (Table 6 Section C); whereas, Hu ***prions*** containing wt PrP.sup.Sc cause disease in Tg(MHu2M)5378/Prnp.sup.0/0 mice at .about.190 d (Table 6 Section B). The onset of illness in. . .

DETD Tg(MHu2M-P101L) mice inoculated with GSS ***prions*** exhibited spongiform degeneration and reactive astrocytic gliosis similar to uninoculated Tg(MHu2M-P101L) mice that developed CNS dysfunction spontaneously. However, the inoculated. . . accumulation was more intense in some gray matter regions such as the hippocampus in the Tg(MHu2M-P101L) mice inoculated with GSS ***prions*** than the uninoculated animals exhibiting spontaneous illness.

DETD . . . DeArmond S. J., and Prusiner, S. B. (1994). Ser. transmission in rodents of neurologic disease from transgenic mice expressing mutant ***prion*** protein. Likewise, the brain of the GSS patient JJ from which the inoculum was derived contained relatively little or no. . . J., Poulter, M., Owen, F., Terwilliger, J. D., Westaway, D., Ott, J., and Prusiner, S. B. (1989). Linkage of a ***prion*** protein missense variant to Gerstmann-Straussler syndrome. Nature 338:342-345. On some occasions, a weak, diffuse band comigrating with PrP 27-30 has. . . of CNS dysfunction. The relatively short incubation times in the Tg(MHu2M-P101L)69/Prnp.sup.0/0 mice argue that the brain of JJ contained high ***prion*** titers even if PrP 27-30 was difficult to detect. From these results, we conclude that PrP.sup.Sc containing the P102L mutation. . .

DETD Transmission of Familial CJD (E200K) Human ***Prions*** To Tg(MHu2M) Mice

DETD . . . (\pm SEM, n=10) for the LJ1 case and .about.160 d for the CA case. In contrast to the P102L mutation, Hu ***prions*** from patients who carried the E200K mutation caused disease as rapidly in Tg(MHu2M)5378/Prnp.sup.0/0 mice as Hu ***prions*** containing wtPrP.sup.Sc from sporadic CJD cases (Table 6 Section C).

DETD Transgenic mice expressing moderate to high levels of wild-type human ***prion*** (HuPrP (SEQ ID NO:2)) were originally constructed by microinjecting fertilized FVB embryos with cosmid DNA expressing human PrP. The results of a large number of transmission experiments with sporadic, iatrogenic and familial ***prion*** cases revealed that these mice were no more responsive to human ***prions*** than their non-transgenic counterparts. We have demonstrated that by eliminating

endogenous mouse (Mo)PrP (SEQ ID NO:1) expression in these transgenic mice, transmission of human ***prions*** becomes efficient with mean incubation times as low as 160 days. Expression of even half the normal amount of mouse PrP (SEQ ID NO:1) was sufficient to inhibit human ***prion*** propagation. These results demonstrate that Mo PrP (SEQ ID NO: 1) is extremely inhibitory for the propagation of human ***prions*** in transgenic mice even though the level of expression of HuPrP (SEQ ID NO: 2) was approximately 8 to 16-fold. . . experiments have led to the notion that a third component, which we refer to as protein X, must feature in ***prion*** propagation. Evidence points to the C-terminal region of PrP as the location for the protein X binding site.

DETD The results of these experiments demonstrate that current transgenic mouse models for the assay of human ***prions*** can be improved upon substantially. Because of the inhibitory effects of MoPrP (SEQ ID NO: 1) in mice expressing heterologous. . . is crucial for the efficient propagation of heterologous transgenes, eliminating its expressing is crucial for the efficient propagation of heterologous ***prions*** in these transgenic mice. This can be achieved in one of several ways.

DETD . . . in which the sequence for this binding site is mutated. Such a benign MoPrP molecule will not interfere with human ***prion*** propagation in transgenic mice expressing HuPrP (SEQ ID NO: 2) because protein X is not sequestered by the mutant MoPrP.. .

DETD Further modifications of the current transgenic mouse models for the assay of human ***prions*** involve the production of transgenic mice expressing HuPrP (SEQ ID NO: 1) under the control of promoter/enhancer sequences from genes. . . will result in levels of expression much higher than normally achieved by PrP promoter/enhancer sequences leading to greatly shortened human ***prion*** incubation times in transgenic mice expressing these constructs. Alternatively, by creating several lines of transgenic mice in which HuPrP (SEQ. . .

DETD Mice Expressing Multiple PrP Different Transgenes To Increase The Range Of ***Prions*** To Which They Are Susceptible

DETD . . . from patients with polymorphisms and/or with mutations at particular amino acid residues of HuPrP. We have recently discovered that human ***prion*** propagation, at least in the case of the polymorphism at codon 129 and the GSS mutation at codon 102, occurs. . transgene. By creating a line in which a number of different forms of HuPrP (SEQ ID NO: 2) are expressed, ***prions*** with a variety of different polymorphisms and/or mutations are transmitted efficiently to the same host.

DETD TABLE 8

Recipient Mouse	***Prion*** incubation times in Tg (MOPrP-A) mice
	Incubation
	Times mean
	d .+-. SEM
	(n/no)
Inoculum.sup.a	
Illness.sup.b	
Death.sup.c	

(A) Tg(PrP-A) mice

Tg (MOPrP-A). . .

DETD Above we have described using homogenized brain tissue from human patients dying of human ***prion*** disease, either sporadic or iatrogenic Creutzfeld-Jacob Disease (CJD). By inoculating mice of the invention we have shown that it is. . .

DETD . . . the MHu2MPrP transgene in the ablated endogenous PrP background

provides shorter incubation times when the mice were inoculated with human ***prions*** due to the elimination of the interfering effects of endogenous mouse PrP expression. Attempts to breed these 5378/Abl lines to. . .

DETD . . . was run and the transgenic mice were inoculated with homogenized brain material from a human that did not die from ***prion*** related disease but rather from amyotrophic lateral sclerosis (ALS). Mice inoculated with this material did not show symptoms after 530. . .

DETD . . . order to more closely focus on the particular codons within the PrP gene which are related to the development of ***prion*** disease additional chimeric human/mouse PrP genes were created. The three new chimeric constructs are referred to as MHu3, Hu3M and. . .

DETD The most common form of inherited human ***prion*** disease involves a mutation at codon 200 of the PrP gene. This mutation results in the replacement of the amino. . .

DETD . . . 5378/Abl hybrid transgenic mice with familial CJD with codon 178 mutation has not resulted in the demonstration of symptoms of ***prion*** disease after 280 days. These experiments further emphasize the importance of codon 129 with respect to the transmissibility of human ***prion*** disease.

DETD . . . homology between PrP^{sup.Sc} in the inocula and the transgene-expressed PrP appears to be necessary for a efficient transmission of human ***prions*** to the transgenic mice. Specifically, the mice Tg(MHu2M-P101L)69/Abl did demonstrate symptoms apparently due to the mutation at codon 101 which matched the mutation of the humans who died of ***prion*** disease.

DETD . . . in the PrP gene of a transgenic mouse are desirable when using the transgenic mice to detect the presence of ***prions*** from a specific infected individual. More specifically, it can be seen that it is desirable to construct a chimeric gene. . . human PrP (SEQ ID NO: 2) gene) which point mutation matches a natural mutation in an individual who died of ***prion*** infection and whose brain tissue is used as inoculant in the transgenic mouse. By matching the mutation in the PrP. . . with the mutation in the individual from whom the inoculant is obtained it is possible to detect the presence of ***prions*** in the inoculant. Thus, a transgenic mouse with several different PrP genes (each with a different codon mutation) or a. . . (codon) mutations would be expected to develop disease when inoculated with an inoculant containing all or any one of the ***prions*** from individuals with different genetic mutations in the PrP gene.

DETD . . . experiments. The lines are referred to as Tg(HuPrP, V129)152/FVB and 110/FVB. In general, the success rate in transmission of human ***prions*** to these transgenic mice was found to be no higher than transmission of human ***prions*** to non-transgenic mice. It is pointed out that these mice do not have an ablated endogenous PrP gene and do. . . one inoculum wherein the inoculum was obtained from an individual dying of iCJD. This inoculum was capable of transmitting human ***prions*** to mice at a rate of about 2 in 10 after 589 days.

DETD The transgenic mice described above which included the entire human PrP gene were not susceptible to infection with human ***prions*** as shown within Table 13. However, these mice were crossed with mice having an ablated PrP gene to produce hybrid. . . as Tg(HuPrP, V129)152/Abl mice. The results are shown below in Table 14 indicating that it was possible to transmit human ***prions*** to these hybrid mice having the endogenous PrP gene ablated.

DETD . . . These mice were referred to as Tg(HuPrP, M129)440/Abl. These mice demonstrated a very short incubation time when inoculated with human ***prions***. It would be expected that by breeding these mice to produce homozygous mice would further reduce the incubation time.

DETD . . . SEQUENCE CHARACTERISTICS:

(A) LENGTH: 254 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(vi) ORIGINAL SOURCE:
(A) ORGANISM: MOUSE ***PRION*** PROTEIN, MoPrP
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
MetAlaAsnLeuGlyTyrTrpLeuLeuAlaLeuPheValThrMetTrp
151015
ThrAspValGlyLeuCysLysLysArgProLysProGlyGlyTrpAsn
202530
ThrGlyGlySerArgTyrProGlyGlnGlySerProGlyGlyAsnArg
354045
TyrProProGlnGlyGlyThrTrpGlyGlnProHisGlyGlyGlyTrp
505560
GlyGlnProHisGlyGlySerTrpGlyGlnProHisGlyGlySerTrp
65707580
GlyGlnProHisGlyGlyGlyTrpGlyGlnGlyGlyGlyThrHisAsn
859095
GlnTrpAsnLysProSerLysProLysThrAsnLeuLysHisValAla
100105110
GlyAlaAlaAlaAlaGlyAlaValValGlyGlyLeuGlyGlyTyrMet
115120125
LeuGlySerAlaMetSerArgProMetIleHisPheGlyAsnAspTrp
130135140
GluAspArgTyrTyrArgGluAsnMetTyrArgTyrProAsnGlnVal
145150155160
TyrTyrArgProValAspGlnTyrSerAsnGlnAsnAsnPheValHis
165170175
AspCysValAsnIleThrIleLysGlnHisThrValThrThrThrThr
180185190
LysGlyGluAsnPheThrGluThrAspValLysMetMetGluArgVal
195200205
ValGluGlnMetCysValThrGlnTyrGlnLysGluSerGlnAlaTyr
210215220
TyrAspGlyArgArgSerSerSerThrValLeuPheSerSerProPro
225230235240
ValIleLeuLeuIleSerPheLeuIlePheLeuIleValGly
245250

DETD . . . SEQUENCE CHARACTERISTICS:

(A) LENGTH: 253 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(vi) ORIGINAL SOURCE:
(A) ORGANISM: HUMAN ***PRION*** PROTEIN, HuPrP
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:
MetAlaAsnLeuGlyCysTrpMetLeuValLeuPheValAlaThrTrp
151015
SerAspLeuGlyLeuCysLysLysArgProLysProGlyGlyTrpAsn
202530
ThrGlyGlySerArgTyrProGlyGlnGlySerProGlyGlyAsnArg
354045
TyrProProGlnGlyGlyGlyGlyTrpGlyGlnProHisGlyGlyGly
505560
TrpGlyGlnProHisGlyGlyGlyTrpGlyGlnProHisGlyGlyGly
65707580
TrpGlyGlnProHisGlyGlyGlyTrpGlyGlnGlyGlyGlyThrHis

859095
 SerGlnTrpAsnLysProSerLysProLysThrAsnMetLysHisMet
 100105110
 AlaGlyAlaAlaAlaAlaGlyAlaValValGlyGlyLeuGlyGlyTyr
 115120125
 MetLeuGlySerAlaMetSerArgProIleIleHisPheGlySerAsp
 130135140
 TyrGluAspArgTyrTyrArgGluAsnMetHisArgTyrProAsnGln
 145150155160
 ValTyrTyrArgProMetAspGluTyrSerAsnGlnAsnAsnPheVal
 165170175
 HisAspCysValAsnIleThrIleLysGlnHisThrValThrThrThr
 180185190
 ThrLysGlyGluAsnPheThrGluThrAspValLysMetMetGluArg
 195200205
 ValValGluGlnMetCysIleThrGlnTyrGluArgGluSerGlnAla
 210215220
 TyrTyrGlnArgGlySerSerMetValLeuPheSerSerProProVal
 225230235240
 IleLeuLeuIleSerPheLeuIlePheLeuIleValGly
 245250
 DETD . . . SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 263 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: peptide
 (vi) ORIGINAL SOURCE:
 (A) ORGANISM: BOVINE ***PRION*** PROTEIN, BoPrP
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:
 MetValLysSerHisIleGlySerTrpIleLeuValLeuPheValAla
 151015
 MetTrpSerAspValGlyLeuCysLysLysArgProLysProGlyGly
 202530
 TrpAsnThrGlyGlySerArgTyrProGlyGlnGlySerProGlyGly
 354045
 AsnArgTyrProProGlnGlyGlyGlyGlyTrpGlyGlnProHisGly
 505560
 GlyGlyTrpGlyGlnProHisGlyGlyGlyTrpGlyGlnProHisGly
 65707580
 GlyGlyTrpGlyGlnProHisGlyGlyGlyTrpGlyGlnProHisGly
 859095
 GlyGlyGlyTrpGlyGlnGlyGlyThrHisGlyGlnTrpAsnLysPro
 100105110
 SerLysProLysThrAsnMetLysHisValAlaGlyAlaAlaAlaAla
 115120125
 GlyAlaValValGlyGlyLeuGlyGlyTyrMetLeuGlySerAlaMet
 130135140
 SerArgProLeuIleHisPheGlySerAspTyrGluAspArgTyrTyr
 145150155160
 ArgGluAsnMetHisArgTyrProAsnGlnValTyrTyrArgProVal
 165170175
 AspGlnTyrSerAsnGlnAsnAsnPheValHisAspCysValAsnIle
 180185190
 ThrValLysGluHisThrValThrThrThrThrLysGlyGluAsnPhe
 195200205
 ThrGluThrAspIleLysMetMetGluArgValValGluGlnMetCys
 210215220
 ValThrGlnTyrGlnLysGluSerGlnAlaTyrTyrAspGlnGlyAla
 225230235240
 SerValIleLeuPheSerSerProProValIleLeuLeuIleSerPhe

245250255

LeullePheLeulleValGly

260

DETD . . . SEQUENCE CHARACTERISTICS:

(A) LENGTH: 255 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(vi) ORIGINAL SOURCE:

(A) ORGANISM: SHEEP ***PRION*** PROTEIN, ShPrP

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

MetValLysSerHisIleGlySerTrpIleLeuValLeuPheValAla

151015

MetTrpSerAspValGlyLeuCysLysLysArgProLysProGlyGly

202530

TrpAsnThrGlyGlySerArgTyrProGlyGlnGlySerProGlyGly

354045

AsnArgTyrProProGlnGlyGlyGlyGlyTrpGlyGlnProHisGly

505560

GlyGlyTrpGlyGlnProHisGlyGlyGlyTrpGlyGlnProHisGly

65707580

GlySerTrpGlyGlnProHisGlyGlyGlyGlyTrpGlyGlnGlyGly

859095

SerHisSerGlnTrpAsnLysProSerLysProLysThrAsnMetLys

100105110

HisValAlaGlyAlaAlaAlaAlaGlyAlaValValGlyGlyLeuGly

115120125

GlyTyrMetLeuGlySerAlaMetSerArgProLeulleHisPheGly

130135140

AsnAspTyrGluAspArgTyrTyrArgGluAsnMetTyrArgTyrPro

145150155160

AsnGlnValTyrTyrArgProValAspGlnTyrSerAsnGlnAsnAsn

165170175

PheValHisAspCysValAsnIleThrValLysGlnHisThrValThr

180185190

ThrThrThrLysGlyGluAsnPheThrGluThrAspIleLysIleMet

195200205

GluArgValValGluGlnMetCysIleThrGlnTyrGlnArgGluSer

210215220

GlnAlaTyrTyrGlnArgGlyAlaSerValIleLeuPheSerSerPro

225230235240

ProValIleLeuLeulleSerPheLeullePheLeulleValGly

245250255

CLM What is claimed is:

. . . and said genome having operatively inserted therein all exogenous non-mouse PrP gene; wherein the mouse is susceptible to infection with ***prions*** which generally only infect a genetically diverse mammal due to the presence of the exogenous PrP gene and ablated endogenous PrP gene and further wherein the mouse exhibits symptoms of ***prion*** disease within 200 days or less after inoculation with ***prions*** which generally only infect a genetically diverse mammal.

8. A method of determining the presence of infectious ***prions*** in a sample obtained from a bovine; comprising: obtaining sample tissue from a bovine to be tested; inoculating the transgenic mouse of claim 6 with the sample; and observing the transgenic mouse for symptoms of ***prion*** disease.

. . . said genome has operatively inserted therein an exogenous non-mouse

PrP gene; wherein the transgenic mouse is susceptible to infection with ***prions*** which generally only infect a genetically diverse mammal due to the presence of the exogenous, non-mouse PrP gene and ablated endogenous mouse PrP gene, and further wherein the mouse exhibits symptoms of ***prion*** disease within 200 days or less after inoculation with ***prions*** which generally only infect a genetically diverse mammal.

. . . further having an exogenous, non-mouse PrP gene in its genome; wherein the second transgenic mouse is susceptible to infection with ***prions*** which generally only infect a genetically diverse mammal due to the presence of the exogenous, non-mouse PrP gene and ablated endogenous mouse PrP gene, and further wherein the mouse exhibits symptoms of ***prion*** disease within 200 days or less after inoculation with ***prions*** which generally only infect a genetically diverse mammal.

L12 ANSWER 23 OF 23 USPATFULL on STN

AN 1998:65517 USPATFULL

TI Method of detecting ***prions*** in a sample and transgenic animal used for same

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PA The Regents of the University of California, Alameda, CA, United States (U.S. corporation)

PI US 5763740 19980609

AI US 1995-509261 19950731 (8)

RLI Continuation-in-part of Ser. No. US 1994-242188, filed on 13 May 1994, now patented, Pat. No. US 5565186

DT Utility

FS Granted

EXNAM Primary Examiner: Stanton, Brian R.

LREP Bozicevic & Reed LLP, Bozicevic, Karl

CLMN Number of Claims: 13

ECL Exemplary Claim: 1

DRWN 5 Drawing Figure(s); 4 Drawing Page(s)

LN.CNT 2464

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention includes an artificial PrP gene, a transgenic animal containing a PrP gene of another animal or the artificial PrP gene, a hybrid non-human mammal with an ablated endogenous ***prion*** gene and exogenous ***prion*** gene and assay methodology which uses the animals to detect pathogenic ***prions*** in a sample or diagnose a cause of death. The artificial gene includes a sequence such that when it is inserted into the genome of a host animal (such as a mouse), the animal is rendered susceptible to infection with ***prions*** which normally would infect only a genetically diverse test animal (such as human, cow or sheep). The artificial PrP gene may be comprised of a completely artificial polynucleotide sequence. Alternatively, the artificial gene may be comprised of the codon sequence of a host animal with one or more codon substitutions being made wherein the substitutions are preferably corresponding PrP gene codons from a genetically diverse test animal. Pathogenic ***prions*** in a sample can be detected by injecting the sample to be tested into a transgenic mouse which includes the different codons of the ***prion*** protein gene of the animal (e.g. human) in danger of infection from ***prions*** in the sample.

TI Method of detecting ***prions*** in a sample and transgenic animal used for same

AB . . . containing a PrP gene of another animal or the artificial PrP gene, a hybrid non-human mammal with an ablated endogenous ***prion*** gene and exogenous ***prion*** gene and assay methodology which uses the animals to detect pathogenic ***prions*** in a sample or diagnose a cause of death. The artificial gene includes a sequence such that when it is . . . inserted into the genome of a host animal (such as a mouse), the animal is rendered susceptible to infection with ***prions*** which normally would infect only a genetically diverse test animal (such as human, cow or sheep). The artificial PrP gene. . . codon substitutions being made wherein the substitutions are preferably corresponding PrP gene codons from a genetically diverse test animal. Pathogenic ***prions*** in a sample can be detected by injecting the sample to be tested into a transgenic mouse which includes the different codons of the ***prion*** protein gene of the animal (e.g. human) in danger of infection from ***prions*** in the sample.

SUMM . . . animals used in such assays. More specifically, this invention relates to artificial and chimeric PrP genes, assaying samples for pathogenic ***prions***, and to transgenic mice and hybrid transgenic mice which can be infected which ***prions*** which generally only infect a genetically diverse species.

SUMM ***Prions*** are infectious pathogens that cause central nervous system spongiform encephalopathies in humans and animals. ***Prions*** are distinct from bacteria, viruses and viroids. The predominant hypothesis at present is that no nucleic acid component is necessary for infectivity of ***prion*** protein. Further, a ***prion*** which infects one species of animal (e.g., a human) will not infect another (e.g., a mouse).

SUMM A major step in the study of ***prions*** and the diseases that they cause was the discovery and purification of a protein designated ***prion*** protein ("PrP") [Bolton et al., Science 218:1309-11 (1982); Prusiner et al., Biochemistry 21:6942-50 (1982); McKinley et al., Cell 135:57-62 (1983)]. Complete ***prion*** protein-encoding genes have since been cloned, sequenced and expressed in transgenic animals. PrP.sup.C is encoded by a single-copy host gene. . . et al., Cell 46:417-28 (1986)] and is normally found at the outer surface of neurons. A leading hypothesis is that ***prion*** diseases result from conversion of PrP.sup.C into a modified form called PrP.sup.Sc. However, the actual biological or physiological function of. . .

SUMM It appears that the scrapie isoform of the ***prion*** protein (PrP.sup.Sc) is necessary for both the transmission and pathogenesis of the transmissible neurodegenerative diseases of animals and humans. See Prusiner, S. B., "Molecular biology of ***prion*** disease," Science 252:1515-1522 (1991). The most common ***prion*** diseases of animal are scrapie of sheep and goats and bovine spongiform encephalopathy (BSE) of cattle [Wilesmith, J. and Wells, Microbiol. Immunol. 172:21-38 (1991)]. Four ***prion*** diseases of humans have been identified: (1) kuru, (2) Creutzfeldt-Jakob Disease (CJD), (3) Gerstmann-Strassler-Scheinker Disease (GSS), and (4) fatal familial. . . (FFI) [Gajdusek, D. C., Science 197:943-960 (1977); Medori et al., N. Engl. J. Med. 326:444-449 (1992)]. The presentation of human ***prion*** diseases as sporadic, genetic and infectious illnesses initially posed a conundrum which has been explained by the cellular genetic origin. . .

SUMM . . . While the most reliable transmission data has been said to emanate from studies using non-human primates, some cases of human ***prion*** disease have been transmitted to rodents but apparently with less regularity [Gibbs, Jr. et al., Slow Transmissible Diseases of the. . . Vol. 2, S. B. Prusiner and W. J. Hadlow, eds. (New York: Academic Press), pp. 87-110 (1979); Tateishi et al., ***Prion*** Diseases of Humans and Animals, Prusiner et al., eds. (London: Ellis Horwood), pp. 129-134 (1992)].

SUMM The infrequent transmission of human ***prion*** disease to rodents

has been cited as an example of the "species barrier" first described by Pattison in his studies. . . and M. P. Alpers, eds. (Washington, D.C.: U.S. Government Printing), pp. 249-257 (1965)]. In those investigations, the initial passage of ***prions*** from one species to another was associated with a prolonged incubation time with only a few animals developing illness. Subsequent. . .

SUMM . . . al., Proc. Natl. Acad. Sci. USA 83:6372-6376 (1986)].

Tg(SHaPrP) mice expressing SHaPrP had abbreviated incubation times when inoculated with SHa ***prions***. When similar studies were performed with mice expressing the human, or ovine PrP transgenes, the species barrier was not abrogated, . . . and the incubation times were unacceptably long. Thus, it has not been possible, for example in the case of human ***prions***, to use transgenic animals (such as mice containing a PrP gene of another species) to reliably test a sample to determine if that sample is infected with ***prions***. The seriousness of the health risk resulting from the lack of such a test is exemplified below.

SUMM . . . now although the seemingly remote possibility has been raised that increased expression of wtPrP^{sup.C} stimulated by high HGH might induce ***prion*** disease [Lasmezas et al., Biochem. Biophys. Res. Commun. 196:1163-1169 (1993)]. That the HGH prepared from pituitaries was contaminated with ***prions*** is supported by the transmission of ***prion*** disease to a monkey 66 months after inoculation with a suspect lot of HGH [Gibbs, Jr. et al., N. Engl. J. Med. 328:358-359 (1993)]. The long incubation times associated with ***prion*** diseases will not reveal the full extent of iatrogenic CJD for decades in thousands of people treated with HGH worldwide.. . . Lancet 340:24-27 (1992)]. These cases of iatrogenic CJD underscore the need for screening pharmaceuticals that might possibly be contaminated with ***prions***.

SUMM . . . of such, there clearly is a need for a convenient, cost-effective assay for testing sample materials for the presence of ***prions*** which cause CJD. The present invention offers such an assay.

SUMM . . . are the offspring of different transgenic animals with each other or with a transgenic animal that has an ablated endogenous ***prion*** gene, and assay methodology which uses the transgenic and hybrid animals to detect pathogenic ***prions*** in a sample. The artificial gene includes a sequence such that when it is inserted into the genome of an animal (such as a mouse), the animal is rendered susceptible to infection with ***prions*** which normally would infect only a specific species of genetically diverse animal (such as a human, cow, sheep, pig, chicken, . . . resulting from a cross between two transgenic animals and in particular a cross between a transgenic animal containing the entire ***prion*** gene of a genetically diverse animal (e.g., a mouse containing a human ***prion*** gene) and an animal with its endogenous ***prion*** gene disrupted (e.g., a mouse with an ablated ***prion*** gene). Hybrids also specifically include crossing a transgenic animal having a chimeric ***prion*** gene with an animal with its endogenous ***prion*** gene ablated.

SUMM Pathogenic ***prions*** in a sample can be detected by injecting the sample to be tested into a transgenic or hybrid animal. In. . . PrP gene which gene includes a portion of a gene of the animal (e.g. human) in danger of infection from ***prions*** in the sample. For example, Creutzfeldt Jakob Disease (CJD) is a fatal neurodegenerative disease of humans caused by ***prions***. Preferred transgenic (Tg) mice disclosed herein express a chimeric ***prion*** protein (PrP) in which a segment of mouse (Mo) PrP (SEQ ID NO:1) was replaced with the corresponding human (Hu). . . MHu2MPrP, differs from MoPrP by 9 codons between codons 96 and 167. All of the Tg(MHu2MPrP) mice injected with human ***prions*** developed neurologic disease. More

specifically, the transgenic mice of the invention developed the disease .about.200 days after inoculation with brain homogenates from three CJD ***prions***, MHu2MPrP.sup.Sc was formed; in contrast MoPrP.sup.Sc was produced if Mo ***prions*** were inoculated. Tg(MHu2MPrP) mice disclosed herein are useful in the diagnosis, prevention and treatment of human ***prion*** diseases. Transgenic mice containing the artificial PrP gene or elevated levels of expression of a native PrP gene from a genetically diverse animal can be used to test samples for ***prions*** which might infect such animals. The transgenic and hybrid animals disclosed herein consistently develop the adverse effects of such ***prions*** in a relatively short time and are substantially cheaper and easier to maintain than are currently used primate models. Transgenic mice containing a human ***prion*** gene are designated Tg(HuPrP) and may be crossed with mice with an ablated endogenous ***prion*** gene which are designated Prnp.sup.0/0 to obtain a hybrid designated Tg(HuPrP)/Prnp.sup.0/0.

SUMM . . . into the genome of one animal (e.g., a mouse, hamster or rat) will render the mammal susceptible to infections from ***prions*** which naturally only infect a genetically diverse mammal, e.g., human, bovine or ovine.

SUMM Another object of the invention is to provide an assay for the detection of ***prions*** in a sample.

SUMM Another object is to provide a hybrid animal which is obtained by crossing an animal having an ablated endogenous ***prion*** gene with a transgenic animal containing (1) a chimeric gene or (2) the ***prion*** gene of a genetically diverse animal which gene may be present at elevated levels.

SUMM . . . (e.g. a human, cow or sheep) in a manner so as to render the host animal susceptible to infection with ***prions*** which normally infect only the genetically diverse test animal.

SUMM . . . to the PrP gene of the genetically diverse animal which transgenic animal may be used by itself to assay for ***prions*** or for cross-breeding with an animal which has an ablated endogenous ***prion*** gene.

SUMM . . . of the present invention is that the transgenic and hybrid animal can be used to assay for the presence of ***prions*** in a sample in a manner which is substantially faster, more efficient and cheaper than presently available assay methods.

SUMM Another advantage is that transgenic and hybrid animals inoculated with ***prions*** of humans can be used as test animals for testing drugs for efficacy in the treatment of humans suffering from diseases resulting from infection with ***prions***.

SUMM Another advantage is that the transgenic and hybrid animals can detect ***prions*** in a sample at very low levels, e.g., 1 part per million, and even as low as 1 part per . . .

SUMM . . . animals provide an assay which is highly accurate, i.e., does not provide false positives and consistently determines the presence of ***prions***.

SUMM Yet another advantage is that by increasing the copy number of an exogenous ***prion*** gene of the invention in a transgenic or hybrid and/or disrupting the endogenous gene of, the incubation time for ***prion*** caused disease is decreased.

SUMM A feature of the present invention is that the transgenic and hybrid animals injected with a sample containing pathogenic ***prions*** will consistently develop the disease effects of the ***prions*** within a relatively short time, e.g. about 200 days +/-50 days after injection or less.

DETD The term " ***prion*** " shall mean an infectious particle known to cause diseases (spongiform encephalopathies) in humans and animals. The term " ***prion*** " is a contraction of the words "protein" and "infection" and the particles are comprised largely if not exclusively

of PrP^{sup}.Sc molecules encoded by a PrP gene. ***Prions*** are distinct from bacteria, viruses and viroids. Known ***prions*** include those which infect animals to cause scrapie, a transmissible, degenerative disease of the nervous system of sheep and goats as well as bovine spongiform encephalopathies (BSE) or mad cow disease and feline spongiform encephalopathies of cats. Four ***prion*** diseases known to affect humans are (1) kuru, (2) Creutzfeldt-Jakob Disease (CJD), (3) Gerstmann-Strassler-Scheinker Disease (GSS), and (4) fatal familial insomnia (FFI). As used herein ***prion*** includes all forms of ***prions*** causing all or any of these diseases or others in any animals used--and in particular in humans and in domesticated. . .

DETD The term "PrP gene" refers generally to any gene of any species which encodes any form of a ***prion*** protein. Some commonly known PrP sequences are described in Gabriel et al., Proc. Natl. Acad. Sci. USA 89:9097-9101 (1992) which. . .

DETD . . . when included in the genome of a host animal (e.g., a mouse) will render the mammal susceptible to infection from ***prions*** which naturally only infect a genetically diverse test mammal, e.g., human, bovine or ovine. In general, an artificial gene will. . . codon of a genetically diverse mammal (such as a human). The genetically altered mammal being used to assay samples for ***prions*** which only infect the genetically diverse mammal. Examples of artificial genes are mouse PrP genes encoding the sequence as shown. . . associated with any native PrP gene but which, when inserted into an animal render the animal susceptible to infection with ***prions*** which would normally only infect a genetically diverse animal.

DETD The terms "chimeric gene," "chimeric PrP gene", "chimeric ***prion*** gene" and the like are used interchangeably herein to mean an artificially constructed gene containing the codons of a host. . . will, when inserted into the genome of a mammal of the host species, render the mammal susceptible to infection with ***prions*** which normally infect only mammals of the second species. The preferred chimeric gene disclosed herein is MHu2M which contains the. . .

DETD . . . may be any animal for which one wishes to run an assay test to determine whether a given sample contains ***prions*** with which the test animal would generally be susceptible to infection. For example, the test animal may be a human, cow, sheep, pig, horse, cat, dog or chicken, and one may wish to determine whether a particular sample includes ***prions*** which would normally only infect the test animal. This is done by including PrP gene sequences of the test animal into the host animal and inoculating the host animal with ***prions*** which would normally only infect the test animal.

DETD The terms "ablated ***prion*** gene", "disrupted PrP gene", and the like are used interchangeably herein to mean an endogenous ***prion*** gene which has been altered (e.g., add and/or remove nucleotides) in a manner so as to render the gene inoperative. Examples of non-functional ***prion*** genes and methods of making such are disclosed in Bueler, H., et al "Normal development of mice lacking the neuronal. . .

DETD . . . are used interchangeably herein to mean an animal obtained from the cross-breeding of a first animal having an ablated endogenous ***prion*** gene with a second animal which includes either (1) a chimeric gene or artificial ***prion*** gene or (2) a ***prion*** gene from a genetically diverse animal. For example a hybrid mouse is obtained by cross-breeding a mouse with an ablated mouse ***prion*** gene with a mouse containing (1) human ***prion*** genes (which may be present in high copy numbers) or (2) chimeric genes. The term hybrid includes any offspring of a hybrid including inbred offspring of two hybrids provided the resulting offspring is susceptible to infection with ***prions*** with normal infect only a genetically diverse species.

DETD The terms "susceptible to infection" and "susceptible to infection by

prions " and the like are used interchangeably herein to describe a transgenic or hybrid test animal of the invention which has. . . 80% or greater, preferably 98% or greater, and most preferably a 100% chance of developing a disease if inoculated with ***prions*** which would normally only infect a genetically diverse test animal. The terms are used to describe a transgenic or hybrid. . . as a transgenic mouse Tg(MHu2M) which, without the chimeric PrP gene, would not be susceptible to infection with a human ***prion*** (less than 20% chance of infection) but with the chimeric gene is susceptible to infection with human ***prions*** (80% to 100% chance of infection).

DETD The term "incubation time" shall mean the time from inoculation of an animal with a ***prion*** until the time when the animal first develops detectable symptoms of disease resulting from the infection. A reduced incubation time. . .

DETD HuPrP for a human ***prion*** protein;

DETD MoPrP for a mouse ***prion*** protein;

DETD SHaPrP for a Syrian hamster ***prion*** protein;

DETD PrP.sup.Sc for the scrapie isoform of the ***prion*** protein;

DETD MoPrP.sup.Sc for the scrapie isoform of the mouse ***prion*** protein;

DETD Prn-p.sup.0/0 for ablation of both alleles of an endogenous ***prion*** gene, e.g., the MoPrP gene;

DETD Tg(HuPrP)/Prnp.sup.0/0 for a hybrid mouse obtained by crossing a mouse with a human ***prion*** gene (HuPrP) with a mouse with both alleles of the endogenous ***prion*** gene disrupted;

DETD Tg(MHu2M)/Prnp.sup.0/0 for a hybrid mouse obtained by crossing a mouse with a chimeric ***prion*** gene (MHu2M) with a mouse with both alleles of the endogenous ***prion*** gene disrupted.

DETD . . . into the genome of a host animal (e.g. a mouse or hamster) will render the animal susceptible to infection with ***prions*** which normally infect only a genetically diverse test animal (e.g. a human, cow or sheep), thereby including genes wherein one. . . is replaced with a corresponding portion of a human PrP gene thereby rendering the mouse susceptible to infection with human ***prions*** ; (4) a transgenic mammal with elevated levels of expression of a PrP gene of a genetically diverse mammal wherein the. . . a genetically diverse animal; (5) a transgenic hybrid animal which is obtained by crossing a animal having an ablated endogenous ***prion*** gene with an animal with a chimeric gene as per (2) above or an animal with a ***prion*** gene of another genetically diverse animal therein e.g., as per (4) above; (6) a method of determining whether a sample is infected with ***prions*** which method involves inoculating a transgenic or hybrid mammal of the invention with a sample to be tested and observing. . . mammal for a period of time sufficient to determine if the mammal develops symptoms of a disease normally associated with ***prions*** ; (7) a method of testing the efficacy of a drug in the treatment of disease developed as a result of infection with ***prions*** comprising administering a drug to be tested to a transgenic or hybrid animal infected with ***prions*** and observing and/or testing the mammal to determine if the drug aids in treating or slowing the progress of the. . . which has died and observing the transgenic or hybrid animal in order to determine if the animal develops symptoms of ***prion*** infections.

DETD . . . of the invention is to use the animal to test a sample of material to determine if that material has ***prions*** which will infect a human and cause disease.

DETD . . . some instances. More specifically, due to small differences in the protein encoded by the PrP gene of different mammals, a ***prion*** which will infect one mammal (e.g. a human) will not normally infect a different mammal (e.g. a mouse). Due to. . . is not generally possible to use normal, i.e. non-transgenic animals such as

mice to determine whether a particular sample contains ***prions*** which would normally infect a different species of animal such as a human. The present invention solves this problem in. . .

DETD . . . order for the transgenic animals to be useful, it is necessary for the animals to be susceptible to infection with ***prions*** which normally infect only genetically diverse test animals, and in particular animals of commercial significance for testing, such as humans,. . .

DETD . . . the resulting transgenic animal (with a low copy number of human PrP genes) is not susceptible to infection with human ***prions***. Second, when only some of the codons differing between the host and the test animal are switched, the resulting transgenic animal is susceptible to infection with ***prions*** which normally only infect the test animal.

DETD . . . with the PrP gene of a test animal to obtain a useful transgenic animal which is susceptible to infection with ***prions*** which normally only infect the test animal by substantially increasing the copy number of the test animal's PrP gene in. . . of a human in a relatively low copy number (e.g. 1 to 4) is not susceptible to infection with human ***prions***. However, if the transgenic mouse includes a very high copy number of a human gene (e.g. 30-300 copies), the resulting transgenic animal is susceptible to infection with human ***prions***. Further, when a host animal such as a mouse has only a portion of its PrP gene replaced with a. . . corresponding portion of a test animal such as a human, the resulting transgenic animal is highly susceptible to infection with ***prions*** which normally infect only the test animal. This is true even if the chimeric gene is present in the transgenic. . .

DETD Lastly, in order to reduce incubation time hybrid mice were created by crossing mice with ablated ***prion*** genes with transgenic mice which (1) included a ***prion*** gene from a genetically diverse animal e.g., a human or (2) include a chimeric or artificial gene of the present. . .

DETD . . . the copy number tends to decrease the incubation time for the disease once the animal is inoculated with material containing ***prions***. Notwithstanding such, we now understand that, when the copy number is increased to very high numbers (e.g. 100 copies and above), the transgenic animals may spontaneously demonstrate symptoms of ***prion*** disease. Thus, a most preferred transgenic animal of the invention will include a chimeric PrP gene in a sufficiently high. . . adjustments can be made to increase the copy number if the resulting transgenic animals are not subject to infection with ***prions*** which normally infect only a genetically diverse animal. Further, adjustments can be made with respect to the use of specific. . .

DETD . . . the entire PrP gene sequence of the test animal into the host animal and render the host animal susceptible to ***prions*** which normally only infect the test animal. However, such is not the case when the host animal and test animal. . . PrP gene, such as that of a human, the resulting transgenic mouse will not be susceptible to infection with human ***prions*** unless the human gene is present in the mouse in a relatively high copy number.

DETD . . . that the animal would not spontaneously become sick, and yet allow the animal to become sick when inoculated with human ***prions***, we created a chimeric gene which includes only a portion of the human PrP gene in the mouse PrP gene.. . .

DETD When transgenic animals are produced by placing the entire human ***prion*** gene into that of a mouse the resulting transgenic mouse does not become consistently ill in a short period of time when inoculated with ***prions*** which generally only infect humans i.e., is not susceptible to infection with human ***prions***. The inability to become infected appears to be related to the presence of

the endogenous mouse ***prion*** gene. When a mouse with a human ***prion*** gene is crossed with a mouse with a disrupted endogenous mouse gene the hybrid offspring are infected by ***prions*** which normally only infect humans. Such hybrid mice will consistently become infected and exhibit an incubation time of less than. . .

DETD . . . with a long incubation time. While the high cost of caring for nonhuman primates prevented extensive studies of the human ***prion*** diseases, the transmissibility of these diseases stimulated studies of the animal ***prion*** analogues in rodents [Manuelidis et al., Proc. Natl. Acad. Sci. USA 75:3422-3436 (1978); Manuelidis et al., Proc. Natl. Acad. Sci. . .

DETD The present disclosure opens a new frontier in the investigation of the human ***prion*** diseases since transmission studies can now be performed relatively rapidly in genetically altered mammals such as Tg(MHu2M) mice that are relatively inexpensive to maintain. For the first time, endpoint titrations of ***prions*** in multiple human body tissues and fluids can be performed and standard curves constructed for more economical incubation time assays. The information derived from such studies of human ***prions*** will be useful in the management of CJD patients who are thought to pose some risk to relatives, physicians, nurses. . .

DETD In studies of human ***prion*** diseases with apes and monkeys, the use of one or two, or rarely three, animals as recipients for a single. . . significant problem in evaluating the transmissibility of a particular inoculum from an individual patient. The transgenic mice contain a chimeric ***prion*** gene, e.g., Tg(MHu2M) mice, and hybrid mice e.g., Tg(HuPrP)/Pmp.sup.0/0 described here obviate many of the problems created by using nonhuman. . .

DETD These results demonstrate the "universality" of the MHu2M transgene for transmission studies with other types of transgenic animals and other ***prion*** inocula. For example, it may be most efficient to use mice expressing MHu2MPPr transgenes coding for either a methionine or. . .

DETD . . . PrP gene which, when inserted into a host mammal (such as a mouse) renders that mammal susceptible to infection with ***prions*** which normally infect only a genetically diverse test mammal (e.g. a human, cow or sheep). The artificial PrP gene may. . .

DETD . . . segments of the human PrP gene and obtain a transgenic mouse which is subject to being readily infected with human ***prions***. Thus, the invention is not limited to the particular chimeric gene MHu2M or chimeric mice produced using this gene. The. . . types of transgenic Animals which include artificial genes wherein the artificial gene renders the transgenic animal susceptible to infection with ***prions*** which normally infect only a genetically diverse animal.

DETD . . . break the "species barrier" by creating a particular chimeric gene whereby transgenic mice can test for the presence of human ***prions*** we have opened the door for the creation of other transgenic animals which will include other artificial PrP genes which, for example, can allow for the testing for the presence of bovine or ovine ***prions*** in a sample.

DETD Hybrid animals of the invention can be produced by crossing an animal with an ablated endogenous ***prion*** gene with either of the transgenic animals mentioned above. For example, a mouse containing a human/mouse chimeric ***prion*** is crossed with a mouse with a disrupted endogenous ***prion*** gene e.g., Tg(Pmp.sup.0/0). Alternatively, a mouse containing a high copy number of human ***prion*** genes (e.g., 50 +/- 25) is crossed with a mouse with a disrupted endogenous ***prion*** gene e.g., Tg(Pmp.sup.0/0) to obtain a hybrid Tg(HuPrP)/Pmp.sup.0/0. A variety of different hybrids can be obtained by crossing an animal with an ablated ***prion*** gene (i.e., a null ***prion*** background) with different transgenic animals with different ***prion*** genes. When successful hybrids

are obtained they can be crossed to produce other animals which for the purpose of the disclosure are also considered hybrids if they are susceptible to infection with ***prions*** which generally only infect a genetically diverse species.

DETD The incubation time of Tg(MHu2M) mice inoculated with Hu ***prions*** is now about 200 days +/-50 days, which can be reduced substantially by increasing the copy number of the MHu2M. . . transgene expression was found to be inversely proportional to the length of the scrapie incubation time after inoculation with SHa ***prions*** [Prusiner et al., Cell 63:673-686 (1990)]. Thus, producing Tg(MHu2M) mice with higher levels of transgene expression is a means of. . .

DETD . . . a mouse lacking the endogenous mouse PrP gene. We obtained incubation periods of .about.105 days with a heterologous Syrian hamster ***prion*** inoculum, shortening to .about.62 days with a homologous MH2M ***prion*** inoculum. The shortest incubation period so far observed in any of our transgenic mouse studies was .about.45 days for a line expressing the mouse PrP gene. Assuming a similar minimum incubation period with MHu2M ***prions*** in Tg(MHu2M PrP) mice lacking the endogenous mouse PrP gene, we can confidentially expect incubation periods of the order of 45.times.105/62=76 days with human ***prions***. This is a conservative estimate; even shorter incubation periods can be obtained in lines with very high copy numbers. Copy. . . keep the copy number below about 100 in order to avoid producing transgenic animals which become sick without inoculation with ***prions***.

DETD . . . substitutions in other chimeric Hu/Mo PrP constructs, it is possible to further enhance the susceptibility of Tg mice to Hu ***prions*** as reflected by shortened incubation times. Shortening the incubation time is a worthwhile goal for the facilitation of many future studies in ***prion*** research and for the evaluation of pharmaceuticals, foods, tissues, organs, grafts, cosmetics and other substances--particularly substances which have some portion derived from an animal, such as a human, which animal might be infected with ***prions***.

DETD . . . of a chimeric or artificial PrP gene and the incubation time of disease after inoculation of the transgenic animal with ***prions***. Specific MHu2M mice disclosed herein have only 3 or 4 copies of the MHu2M gene. The number of copies can. . .

DETD . . . PrP genes have been determined allowing, in each case, the prediction of the complete amino acid sequence of their respective ***prion*** proteins. The normal amino acid sequence which occurs in the vast majority of individuals is referred to as the wild-type. . . either five or six repeats of an eight amino acid motif sequence in the amino terminal region of the mature ***prion*** protein. While none of these polymorphisms are of themselves pathogenic, they appear to influence ***prion*** diseases. Distinct from these normal variations of the wild-type ***prion*** proteins, certain mutations of the human PrP gene which alter either specific amino acid residues of PrP or the number of octarepeats have been identified which segregate with inherited human ***prion*** diseases.

DETD The fundamental event in ***prion*** propagation seems to be the conversion of PrP^{sup.c}, which contains .about.43% .alpha.-helix and is devoid of .beta.-sheet, into PrP^{sup.Sc} which. . . feature in the formation of PrP^{sup.Sc}. One explanation for the difference in susceptibility of Tg(MHu2M) and Tg(HuPrP) mice to Hu ***prions*** in mice may be that mouse chaperons catalyzing the refolding of PrP^{sup.C} into PrP^{sup.Sc} can recognize MHu2MPrP but not HuPrP. . .

DETD . . . In support of this hypothesis is that rodents also differ from ruminants including sheep and cattle at this site; sheep ***prions*** have failed to transmit neurodegeneration to Tg(ShePrP). In these experiments the transgenic mice expressed the entire sheep PrP gene.

DETD In contrast to Tg(MHu2M) mice, the overall transmission rate of Hu ***prion*** inocula from a wide variety of sources was less than 10% in Tg(HuPrP) mice, no different from the rate observed. . . appears to be a relatively infrequent event similar to the rare conversion of MoPrP.sup.C to PrP.sup.Sc in response to human ***prions***. The low rates of transmission in these mice do not seem to be a consequence of low titers of human ***prion*** titers: two inocula which failed to cause disease in Tg(HuPrP) mice transmitted to 100% of inoculated Tg(MHu2M) animals.

DETD . . . in the presence of MoPrP.sup.C and why HuPrP.sup.C is converted into PrP.sup.Sc in the absence of MoPrP.sup.c. This model of ***prion*** propagation involving protein X can also explain why inherited forms of ***prion*** disease modeled in mice with the GSS mutation at codon 102 can be produced with Tg mice expressing the P102L. . . HuPrP as described here. The proposed model is consistent with additional observations showing that Tg(MHu2M) mice were resistant to Hu ***prions*** from a patient with GSS who carried the P102L mutation but were susceptible to ***prions*** from patients with familial CJD who harbor the E200K mutation; however, Tg(MHu2M-P101L) mice were susceptible to GSS ***prions***. These findings and other studies reported here demonstrate that single amino acid mismatches at codon 102 or 129 prolong the. . .

DETD . . . is likely that a molecular chaperon features in the unfolding of PrP.sup.C and its refolding into PrP.sup.Sc. "Strains" of Human ***Prions***

DETD Studies in rodents have shown that ***prion*** strains produce different patterns of PrP.sup.Sc accumulation [Hecker et al., Genes & Development 6:1213-1228 (1992); DeArmond et al., Proc. Natl. . . by the sequence of PrP.sup.C [Carlson et al., Proc. Natl. Acad. Sci. USA in press (1994)]. The molecular basis of ***prion*** diversity has for many years been attributed to a scrapie specific nucleic acid [Bruce et al., J. Gen. Virol. 68:79-89. . . [Meyer et al., J. Gen. Virol. 72:37-49 (1991); Kellings et al., J. Gen. Virol. 73:1025-1029 (1992)]. Other hypotheses to explain ***prion*** strains include variations in PrP Asn-linked sugar chains [Hecker et al., Genes & Development 6:1213-1228 (1992)] and multiple conformers of. . .

DETD The patterns of PrP.sup.Sc accumulation in the brains of inoculated Tg(MHu2M) mice were markedly different for RML ***prions*** and Hu ***prions***. However, RML ***prion*** inocula containing MoPrP.sup.Sc stimulated the formation of more MoPrP.sup.Sc while Hu ***prion*** inocula containing HuPrP.sup.CJD triggered production of MHu2MPrP.sup.Sc. The distribution of neuropathological changes characterized by neuronal vacuolation and astrocytic gliosis is similar to the patterns of PrP.sup.Sc accumulation in the brains of Tg(MHu2M) mice inoculated with RML ***prions*** or Hu ***prions***.

DETD New Approaches To Investigating Human ***Prion*** Diseases
DETD The remarkable sensitivity of Tg(MHu2M) mice to Hu ***prions*** represents an important advance in neurodegenerative disease research.

Based on the present disclosure regarding chimeric Hu/Mo PrP transgenes we conceived of a similar approach to the construction of Tg mice susceptible to BSE and scrapie sheep ***prions***. Such would be useful in detecting ***prion*** diseases in domestic animals. The importance of animal ***prion*** diseases is illustrated by BSE or "mad cow disease" in Great Britain, where >150,000 cattle have died. This ***prion*** disease BSE is thought to have originated with cattle consuming meat and bone meal produced from sheep offal containing scrapie ***prions*** [Wilesmith, J. W., Semin. Viro. 2:239-245].

DETD . . . sheep scrapie about the risk factors to humans from BSE. Whether any of these seven amino acid substitutions render bovine ***prions*** permissive in humans remains to be established. It may be that Tg(MHu2M) mice are susceptible to bovine as well as sheep

prions . Of perhaps even greater importance, Tg(MHu2M) mice have immediate application in the testing of pharmaceuticals for human ***prion*** contamination. The Tg(MHu2M) mice described here provide a sensitive, reliable and economical bioassay for detecting the presence of human ***prions*** .

DETD Since the fundamental event underlying ***prion*** propagation seems to be a conformational change in PrP [Pan et al., Proc. Natl. Acad. Sci. USA 90:10962-10966 (1993)] and. . . positions out of 254 [Kretzschmar et al., DNA 5:315-324 (1986)], we constructed modified PrP transgenes. Chimeric SHa/Mo transgenes have produced ***prions*** with new properties, the most useful being the chimeric SHa/Mo transgene labeled MH2M which carries 5 amino acid substitutions found. . .

DETD We have found that mice expressing the MHu2M chimeric transgene are susceptible to human ***prions*** after abbreviated incubation times. More specifically, the transgenic mice of the present invention which include the chimeric MHu2M gene will, after inoculation with human ***prions*** , develop disease symptoms attributed to the ***prions*** within about 200 days +/-50 days. Further, 80% or more of the transgenic mice of the invention inoculated with human ***prions*** will develop symptoms of the disease, more preferably 98% or more of the mice will develop symptoms of the disease. According to experiments carried out, 100% of the transgenic MHu2M mice inoculated with human ***prions*** actually developed symptoms of the disease in about 200 days +/-50 days.

DETD . . . neurodegeneration more rapidly than monkeys, they provide a preferred host for bioassays of infectivity in tissues of humans dying of ***prion*** diseases. The Tg(MHu2M) mice disclosed herein provide an excellent system for assessing the sterility of pharmaceuticals as well as tissue and organ grafts prepared from human sources. Other transgenic mice which include the ***prion*** protein gene of the animal in danger of infection can be used to test samples for ***prion*** diseases which can infect domestic animals such as sheep and cattle.

DETD . . . PrP genes can be created which, when inserted into a host animal, will render that animal susceptible to infection with ***prions*** which normally only infect a second and genetically diverse test animal. There are nearly an infinite number of possible artificial. . . would meet the basic criteria of the invention, i.e. rendering a mammal such as a mouse susceptible to infection with ***prions*** which normally infect only a genetically diverse test animal such as a human. The MHu2M gene of the invention is. . . are included. Transgenic mice expressing only low levels of human PrP.sup.C are unlikely to become ill after inoculation with human ***prions*** . However, if the level of human prP.sup.c expression is elevated, the transgenic animals become susceptible to infection with human ***prions*** . This is another means of overcoming the species barrier by what is referred to as a stochastic process.

DETD . . . the resulting gene could be inserted into a mouse in order to render the mouse susceptible to infection with bovine ***prions*** . A similar strategy with respect to producing a mouse which would be susceptible to infection with sheep ***prions*** can be deduced from reviewing FIG. 5. In addition to these possibilities those skilled in the art will recognize that,. . . to obtain a useful artificial gene which, when inserted into an animal, will render that animal susceptible to infection with ***prions*** which normally would infect only a genetically diverse mammal.

DETD . . . mammal will express the PrP gene at a level sufficiently high to render the host animal susceptible to infection with ***prions*** which normally only infect a genetically diverse test animal.

DETD PrP.sup.Sc has been found in the brains of affected Tg(MHu2M) mice after inoculation with Hu(CJD) or Mo(RML) ***prions*** . Brain homogenates

of Tg(MHu2M) were either left undigested or digested with proteinase K (BMB) at a final concentration of 20. . .

DETD The distribution of PrP.sup.C and PrP.sup.Sc in clinically sick Tg(MHu2M) mice inoculated with Mo(RML) and Hu(CJD) ***prions*** were detected by the histoblot method. The histoblots included those of coronal sections through the region of the hippocampus and. . .

DETD . . . of these offspring. As shown in Example 5 below, these mice were found to be susceptible to infection with human ***prions*** 100% of the time.

DETD Sources of ***Prion*** Inocula

DETD . . . clinical diagnosis of CJD or GSS had been confirmed by histopathological examination of brain tissues and, in most cases, by ***prion*** protein analysis. In some cases, the PrP gene was amplified by PCR of DNA isolated from patient blood and the. . .

DETD . . . to X-ray film for 5-60 seconds. .alpha.-PrP RO73 rabbit antiserum was used at a final dilution of 1:5000 and 3F4 ***monoclonal*** antibody was also employed [Serban et al., Neurology 40:110-117 (1990)].

DETD Tg(MHu2MPrP) Mice Are Susceptible to Human ***Prions***

DETD Inoculation of Tg(MHu2M) mice with Mo(RML) ***prions*** passaged in mice produced disease in 178.+-.3 days, which is .about.40 longer than Mo(RML) ***prions*** in non-Tg mice. Prolongation of incubation times in mice expressing non-murine transgenes is well established, and occurs presumably because the. . . conversion of MoPrP.sup.C into MoPrP.sup.Sc [Prusiner et al., Cell 63:673-686 (1990)]. In contrast to Tg(MHu2M) mice, incubation times for RML ***prions*** in Tg(MH2M) mice were the same as those of the non-Tg mice [Scott et al., Cell 73:979-988 (1993)].

DETD TABLE 1

Incubation of human (CJD) and mouse (RML) ***prion***

inocula in Tg(MHu2M)FVB-B5378 mice

Incubation Times

(mean days .+-. SE)

Range

Source Inoculum No..sup.a

(days) Illness

Death.sup.b

Sporadic

RG 8/8 225-249

238 .+-. . . .

DETD Tg(HuPrP) Mice Are Resistant to Human ***Prions***

DETD To determine whether expression of HuPrP (SEQ ID NO:2) in Tg(HuPrP)B6SJL-110 and Tg(HuPrP)FVB-152 conferred susceptibility to human ***prions***, incubation periods were measured after inoculation of Tg(HuPrP) and non-Tg mice with brain extracts from 18 patients that had died. . . 2.5 years, we concluded that the two lines of Tg(HuPrP) mice were no more responsive than non-Tg mice to human ***prions*** (see Table 2 below). The rate of transmission to Tg(HuPrP) mice was 8.3% (14 clinically sick mice out of 169. . . after extremely long incubation periods is compounded by the heightened potential for artifactual results due to low levels of contaminating ***prions*** .

DETD Statistical analysis shows that the frequency of Hu ***prion*** transmission to Tg(MHu2MPrP) mice compared to Tg(HuPrP) and non-Tg mice is highly significant using the Fisher's exact test, p<10.sup.-7 [Mehta et al., J. Am. Stat. Assn. 78: (392) 427-434 (1983)]. When Hu ***prion*** transmission to Tg(HuPrP) mice was compared to non-Tg mice, the frequencies were similar, p=0.79.

DETD To confirm the clinical diagnosis of ***prion*** disease, 5 ill

Tg(HuPrP) and 1 non-Tg mice were sacrificed and brain extracts were examined for the presence of PrP.sup.Sc. . . mice which developed clinical signs after 589 days post-inoculation with iatrogenic CJD inoculum #170. The equivalent transmission rates of human ***prions*** in Tg(HuPrP) and non-Tg mice indicate that this is a rare event with the same frequency of occurrence as the stochastic conversion of MoPrP.sup.C to MoPrP.sup.Sc induced by human ***prions*** .

DETD . . . 3F4-reactive PrP.sup.Sc in the brains of 3 out of the 6 mice analyzed may reflect the difficulty of accurately diagnosing ***prion*** disease in elderly animals. Some of the mice inherited ***prion*** diseases of both humans and Tg mice exhibit little or undetectable levels of protease-resistant PrP; yet, based on transmission studies, their brains contain ***prions*** and they show clear spongiform degeneration [Medori et al., N. Engl. J. Med. 326:444-449 (1992)].

DETD In contrast to Tg(MHu2M) mice, Hu ***prions*** from patient RG have not transmitted to either Tg(HuPrP) or non-Tg mice after >330 days (see Table 2 below). Attempts to transmit preparations enriched for Hu ***prion*** rods prepared from the brain of patient RG have likewise been negative for >300 days. In addition, inoculum from the. . .

DETD TABLE 2

Incubation times in Tg(HuPrP)FVB-152 and Tg(HuPrP)B6SJL-110 mice after inoculation with brain extracts from patients with human ***prion*** diseases

Host	Inoculum	Incubation times (n/.sub.a n.sub.o) (days .+-. SE).sup.b
Tg 152	Sporadic CJD (#87011)	1/10 706
Non-Tg	Sporadic CJD. . .	3/5 697.3 .+-. 51

DETD Some clinically sick Tg(MHu2M) mice inoculated with each of the three CJD ***prion*** inocula or RML ***prions*** were sacrificed for histopathological verification of disease and for ***prion*** protein analysis. Western blots of brain homogenates from Tg(MHu2M) mice infected with Hu ***prions*** probed with RO73 and 3F4 .alpha.-PrP antibodies revealed the presence of protease-resistant PrP.sup.Sc which reacted with the 3F4 ***monoclonal*** antibody showing this protease-resistant product to be MHu2M PrP.sup.Sc. The epitope recognized by this antibody consists of a pair of. . . with MHu2MPrP.sup.Sc as well as HuPrP.sup.C and HuPrP.sup.Sc from diseased human brains. Brain homogenates from Tg(MHu2M) mice infected with RML ***prions*** contained PrP.sup.Sc which was detectable only with RO73 and not 3F4 .alpha.-PrP antibodies, indicating that Tg(MHu2M) mice are capable of producing MoPrP.sup.Sc but not MHu2MPrP.sup.Sc in response to RML ***prions*** previously passaged in mice. While these findings are similar to those reported for Tg(SHaPrP) mice [Scott et al., Cell 59:847-857 (1989)], they contrast with those found for Tg(MH2MPrP) mice where MH2MPrP.sup.Sc was formed in response to RML ***prions*** [Scott et al., Cell 73:979-988 (1993)].

DETD . . . shown in histoblots of coronal brain sections through the hippocampus and thalamus of Tg(MHu2M) mice inoculated with RML or CJD ***prions*** . The weak immunoreactivity of MHu2M PrP with RO73 permitted a degree of analysis which had not been previously possible in. . . react with this antibody. The pattern of PrP.sup.Sc deposition was highly dependent upon the species of origin of the infectious ***prions*** . When inoculated with RML ***prions*** ,

histoblots of the brains of Tg(MHu2M) were similar to those of CD-1 mice infected with RML ***prions***, revealing a diffuse pattern of MoPrP.sup.Sc deposition in the hippocampus, thalamus, hypothalamus and all layers of the neocortex. The histoblot pattern of was strikingly different for Tg(MHu2M) mice inoculated with CJD ***prions***. The deposition of MHu2MPrP.sup.Sc was confined primarily to the deep layers of the neocortex, the thalamus, particularly the ventral posterior. . signal. The same pattern of MHu2MPrP.sup.Sc deposition was consistently observed in histoblots of Tg(MHu2M) mice inoculated with all three CJD ***prion*** isolates prepared from human brain. It is noteworthy that the pattern of MHu2MPrP.sup.Sc deposition is similar to the pattern of. . . Natl. Acad. Sci. USA 89:7620-7624 (1992)]. The spongiform degeneration in the brains of Tg(MHu2M) mice infected with Mo(RML) and Hu(CJD) ***prions*** reflected the patterns of PrP.sup.Sc accumulation described above.

DETD . . . methods are listed in Tables 3-7. With respect to such the (1) methods of making mice; (2) brain homogenates; (3) ***prion*** inocula; (4) measurement of incubation times; (5) immunoblotting; and (6) immunohistochemistry are described below.

DETD . . . at codon 102 of the human PrP gene has ben described Hsiao, K. and Prusiner, S. B. (1990). Inherited human ***prion*** diseases. Neurology 40:1820-1827. ORF cassettes were digested with BglII (which cleaves immediately adjacent to the initiation codon). The 5' protruding. . . to the Sall-cut cosSHa.Tet cosmid expression vector Scott, M. R., Kohler, R., Foster, D., and Prusiner, S. B. (1992). Chimeric ***prion*** protein expression in cultured cells and transgenic mice. Protein Sci. 1:986-997. The isolation of recombinant cosmid clones was achieved by. . . M., Groth D., Foster, D., Torchia, M., Yang, S.-L., DeArmond, S. J., and Prusiner, S. B. (1993). Propagation of ***prions*** with artificial properties in transgenic mice expressing chimeric PrP genes. Cell 73:979-988. NotI fragments, recovered from large-scale DNA cosmid preparations,. . . Walchli, M., Growth, D., Carlson, G., DeArmond, S. J., Westaway, D., and Prusiner, S. B. (1989). Transgenic mice expressing hamster ***prion*** protein produce species-specific infectivity and amyloid plaques. Cell 59:847-857. Genomic DNA isolated from tail tissue of weaning animals was screened. . .

DETD . . . calcium and magnesium ions. For immunoblot analysis, samples were cleared of cell debris by a brief low-speed centrifugation. Purified Hu ***prions*** were prepared using a protocol previously developed for SHa ***prions*** Prusiner et al., (1983) Scrapie ***Prions*** AaAggregate to Form Amyloid-like Birefringent Rods. Cell 35, 349-358.

DETD ***Prion*** Inocula

DETD Human brain specimens were collected from patients dying of sporadic, inherited or infectious ***prion*** disease. The iatrogenic CJD denoted 364 was provided by Dr. John Collinge. The RML isolate from Swiss mice Chandler, R.. . .

DETD . . . of inocula and criteria for diagnosis of scrapie in mice have been described Carlson, G. A., et al., "Linkage of ***prion*** protein and scrapie incubation time genes," Cell 46:503-511 (1986). When clinical signs of CNS dysfunction appeared, the mice were examined. .

DETD . . . proteinase K for 60 min at 37.degree. C. Western blots were performed as described previously Barry, R. A., et al., " ***Monoclonal*** antibodies to the cellular and scrapie ***prion*** proteins," J. Infect. Dis., 154:518-521 (1986); Towbin, H., et al., "Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets:. . .

DETD . . . in 1.3 mM HCl and autoclaved at 121.degree. C. for 10 min Muramoto et al., (1992) The sequential development of ***abnormal***

prion protein accumulation in mice with Creutzfeldt-Jakob disease. Am. J. Pathol. 140, 1411-1420. When temperature decreased, the slides were placed under. . .

DETD Since the Hu ***prion*** inocula are brain homogenates or purified ***prion*** rods from a variety of patients who died of ***prion*** disease, the designations for the patients as well as clinical phenotypes are listed in Table 4 below. The PrP genotypes. . .

DETD TABLE 4

Brain Inocula From Patients Who Died of ***Prion*** Disease

Sporadic Inocula and Infectious CJD ***prions***

Containing wt PrP.sup.Sc

Prion

Human Inoculum

Disease Genotype of PrP.sup.d

PG	sporadic CJD wt, M/M129
EC	sporadic CJD wt, M/M129
MA	sporadic CJD wt, M/M129
PO	sporadic CJD wt, N.D.sup.e
PC	sporadic CJD wt, N.D
364	iatrogenic CJD wt, M/M129

GSS and Familial CJD ***prions*** containing mutant PrP.sup.Sc

JJ GSS P102L, V/V128

LJ-1	familial CJD E200K, M/M129
CA	familial CJD E200K, M/M129
FH	familial CJD E200K, V/M129

.sup.a Substitution. . .

DETD MoPrP.sup.C Inhibits Propagation of Human ***Prions*** in Tg(HuPrP) Mice

DETD When Tg(HuPrP)152/FVB mice and non-Tg littermates were inoculated with Hu ***prions*** from sporadic or iatrogenic CJD as well as inherited ***prion*** disease cases, about 10% of each group of mice developed CNS dysfunction (Telling et al., 1994). Some of the ill mice. . . with polyclonal .alpha.-PrP antiserum that reacts with both Hu (SEQ ID NO:2) and MoPrP (SEQ ID NO:1) and with .alpha.-PrP ***monoclonal*** antibodies (mAb) that react with Hu (SEQ ID NO:2) but not MoPrP (SEQ ID NO:1). Those mice that produced. . .

DETD After Crossing the Tg(HuPrP) 152/FVB Mice onto the Pmp.sup.0/0 Background, They Became Susceptible to Hu ***Prions*** (Table 5)

DETD When Tg(HuPrP) 152/FVB mice were inoculated with Hu ***prions*** from a case of sporadic CJD, referred to as RG, only one Tg mouse out of a group of 10. . .

DETD TABLE 5

Transmission Of Hu ***Prions*** to Tg(HuPrP)/Pmp.sup.0/0 mice

Incubation Time

mean d .+-. SEM

Recipient Mouse Line

Inoculum.sup.a

(n/no)

(A) Tg(HuPrP)FVB

Mice

Tg(HuPrP)152/FVB

sCJD(RG) 721 .+-. 0. . .

DETD . . . highly enriched for PrP^{sup}.Sc prepared from the brain of RG (see Section B of Table 5). Using the .alpha.-PrP 3F4 ***monoclonal*** antibody (mAb) Kacsak, R. J., et al., "Mouse polyclonal and ***monoclonal*** antibody to scrapie-associated fibril proteins," J. Virol. 61:3688-3693 (1987), we estimated, by serial dilution and dot immunoblotting of brain homogenates. . .

DETD . . . of PrP are resistant to scrapie," Cell 73:1339-1347 (1993); Prusiner, S. B., et al., "Immunologic and molecular biological studies of ***prion*** proteins in bovine spongiform encephalopathy," J. Infect. Dis. 167:602-613 (1993); Prusiner, S. B., et al., "Transgenic studies implicate interactions between homologous PrP isoforms in scrapie ***prion*** replication," Cell 63:673-686 (1990), we removed MoPrP^{sup}.C by producing Tg(HuPrP)152/Prnp^{sup}.0/0 mice. When Tg(HuPrP)152/Prnp^{sup}.0/0 were inoculated with Hu ***prions***, they developed signs of neurologic dysfunction with incubation times between 260 and 300 d (Table 5 shown in Section B).

DETD TABLE 6

Transmission of Hu ***prions*** to Tg(MHu2MPrP) mice
Incubation Time
Inoculum^{sup}.a mean d .+-. SEM (n/no)

(A) Tg(MHu2M)/FVB mice inoculated with sporadic or infectious CJD

sCJD(RG) 238 .+-. 3. . .

DETD . . . the length of the incubation time. Although the incubation times are similar for Tg(HuPrP)152/Prnp^{sup}.0/0 and Tg(MHu2M)5378/Prnp^{sup}.0/0 mice inoculated with Hu ***prions*** (Tables 5 and 6 Section B of each), the Tg(HuPrP)152/Prnp^{sup}.0/0 express 5-10-fold more of the transgene product than Tg(MHu2M)5378/Prnp^{sup}.0/0 mice. . . version may be superior to HuPrP in terms of generating mice with the shortest incubation times for bioassays of Hu ***prions***.

DETD Transmission Of Chimeric ***Prions***

DETD . . . significantly to the "species barrier" Prusiner; S. B., et al., "Transgenic studies implicate interactions between homologous PrP isoforms in scrapie ***prion*** replication," Cell 63:673-686 (1990); Scott, M., Foster, D., Mirenda, C., Serban D., Coufal, F., Walchli, M., Growth, D., Carlson, G., DeArmond, S. J., Westaway, D., and Prusiner, S. B. (1989). Transgenic mice expressing hamster ***prion*** protein produce species-specific infectivity and amyloid plaques. Cell 59:847-857. Prolongation of incubation times on primary passage of ***prions*** between species is generally seen while second passage in the same species results in a shortening and stabilization of incubation. . . Monograph 2, D. C. Gajdusek, et al., eds. (Washington, D.C.: U.S. Government Printing), pp. 249-257 (1965). Primary passage of Hu ***prions*** from a sporadic CJD case (EC) produced CNS disease in Tg(MHu2M)5378/FVB with an incubation time of 218.+-.5 d(.+-.SEM) (Table 6. . . Brains from ill mice were collected and homogenates inoculated into mice from the same Tg line. Passage of these chimeric ***prions*** in Tg(MHu2M)5378/FVB mice gave incubation times similar to those seen with Hu ***prions*** on the primary passage (Table 7 Section A). This finding shows that these Tg(MHu2M)5378/FVB mice are completely permissive for Hu ***prions***. Passage of chimeric ***prions*** in Tg(MHu2M)5378/Prnp^{sup}.0/0 mice resulted in a shortening of the incubation time by .about.20% presumably due to the elimination of MoPrP^{sup}.C; i.e., ablating the endogenous mouse ***prion*** gene.

DETD TABLE 7

Serial transmission of chimeric Hu/Mo ***prions*** in Tg(MHu2M)

mice.

Recipient Mouse Line	Inoculum	sup.a	Incubation Times mean d .+-. SEM (n/no)	Illness	Death
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(A) Chimeric ***prions*** produced in Tg(MHu2M) mice inoculated with CJD ***prions***

Tg(MHu2M)5378/	MHu2M(sCJD).sup.b	220 .+-. 3 (7/7).sup.c	226 .+-. 1(5)		
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FVB

Non-Tg5378/FVB	MHu2M(sCJD).sup.b	>340			
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Tg(MHu2M)5378/	MHu2M(sCJD).sup.d	226 .+-. 3 (9/9)	228 .+-. 1(6)		
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FVB

Non-Tg5378/FVB	MHu2M(sCJD).sup.d	>340			
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Tg(MHu2M)5378/	MHu2M(sCJD).sup.d	189 .+-. 4 (8/8)	192 .+-. 1(4)		
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Prnp.sup.0/0

Tg(MHu2M)5378/	MHu2M(sCJD)d	183 .+-. 5 (7/7)	190 .+-. 3(4)		
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Prnp.sup.0/0

(B) Mouse ***prions*** produced in Tg(MHu2M) or non-Tg mice inoculated with RML ***prions***

Tg(MHu2M)5378/	Mo(RML)	178 .+-. 3 (19/19)	203 .+-. (14).sup.e		
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FVB

NonTg5378/FVB	Mo(RML)	127 .+-. 2 (18/18)	156 .+-. 2(5)		
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Tg(MHu2M)5378/	MHu2M(RML).sup.f	185 .+-. 1. . . >300			
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Prnp.sup.0/0

.sup.a Notation in parentheses indicate inoculum used in initial passage in Tg(MHu2M) mice.

.sup.b Mice were inoculated with chimeric ***prions*** generated in the brain o

a Tg(MHu2M)5378/FVB mouse that had been inoculated with a brain homogenat prepared from patient EC. . . of mice developing CNS illness divided by the number

inoculated are given in parentheses.

.sup.d Mice were inoculated with chimeric ***prions*** generated in the brain o

a second Tg(MHu2M)5378/FVB mouse that had been inoculated with a brain

homogenate prepared from patient EC who died of sporadic CJD.

.sup.e Data from (Telling et al. 1994).

.sup.f Mice were inoculated with Mo ***prions*** generated in the brain of

a

Tg(MHu2M)5378/FVB mouse that had been inoculated with RML Mo ***prions*** .

.sup.g Mice were inoculated with Mo ***prions*** generated in the brain of

a

second Tg(MHu2M)5378/FVB mouse that had been inoculated with RML Mo

prions .

DETD Specificity Of Chimeric ***Prions*** And Transgenes

DETD Non-Tg5378/FVB littermates, which express only MoPrp.sup.C, inoculated with the chimeric ***prions*** have remained well for >340 days.

Thus it appears that homology between the substrate Prp.sup.C and the product Prp.sup.Sc in the region bounded by residues 96 to 167 is essential for ***prion*** propagation. Conversely,

Tg(MHu2M)Prp.sup.0/0 mice are resistant to Mo ***prions*** ; they have remained well for >340 days after inoculation (Table 7 Section B).

DETD Although Tg(MHu2M)5378/FVB mice are permissive for Mo(RML)

prions , the incubation time of 178.+-.3 d(+-.SEM) was

protracted compared to that of 127.+-.2 d(+-.SEM) for non-Tg5378/FVB littermates (Table 7 Section B). Two homogenates derived from

Tg(MHu2M)5378/FVB mice were inoculated with Mo(RML) ***prions***

were passaged in Tg(MHu2M)5378/FVB mice and non-Tg littermates. The incubation time in the Tg(MHu2M)5378/FVB mice did not change while the

incubation time in the non-Tg mice shortened to the incubation time registered for primary passage of Mo(RML) ***prions*** in these mice

(Table 7 Section B). This behavior and the fact that MoPrp.sup.Sc is made in response to inoculation with Mo ***prions*** (Telling et

al., 1994) appears to show that Tg(MHu2M)5378/FVB mice propagate Mo

prions from endogenous MoPrp.sup.C and not from MHu2MPrp.sup.C .

DETD In Caucasians (Palmer et al., 1991) but not Asians (Tateishi and

Kitamoto, 1993) Developments in diagnosis for ***prion*** diseases.

Br. Med. Bull. 49,971-979 homozygosity for M or V codon 129 has been reported to predispose people to development of sporadic CJD.

Homozygosity at codon 129 in some Baker et al., (1991) Amino acid polymorphism in human ***prion*** protein and age at death in inherited ***prion*** disease. Lancet 337, 1286; Goldfarb, L. G., et

al., "The molecular genetics of human transmissible spongiform encephalopathy", ***Prion*** Diseases of Humans and Animals, S. B.

Prusiner et al., eds. (London: Ellis Horwood), pp. 139-153 (1992) but not other inherited ***prion*** diseases diminished the age of onset

of CNS dysfunction; Gabizon et al., (1993) Mutation and polymorphism of the ***prion*** protein gene in Libyan Jews with Creutzfeldt-Jakob

disease. Am. J. Hum. Genet 33, 828-835. The Tg(HuPrP)152 mice express HuPrP with. . . another line Tg(HyPrP)440 synthesizes HuPrP (SEQ ID

NO:2) with M at 129. When Tg(HuPrP)152/Prp.sup.0/0 and Tg(HuPrP)440/Prp.sup.0/0 mice were inoculated with ***prions***

from iatrogenic and sporadic cases, the shortest incubation times occurred when the amino acid residues at position 129 were the. . .

DETD The successful transmission of Hu ***prions*** to Tg(MHu2M)5378/FVB

mice promoted us to produce Tg(MHu2M-P101L) 69/Prp.sup.0/0 mice. Unlike the Tg(HuPrP-P102L) mice, these Tg(MHu2M-P101L) mice spontaneously

developed neurologic. . .

DETD Transmission Of GSS Human ***Prions*** To Tg(MHu2M-P101L) Mice

DETD . . . attempted to determine whether the illness would appear more

rapidly if the animals are inoculated. Both wt and GSS Hu ***prions***

were inoculated. Tg(MHu2M-P101L)69Prp.sup.0/0 mice were inoculated at about 70 days of age with brain extract from a GSS patient referred. . .

. mutation, or with brain extracts from two sporadic CJD cases (RG and EC in Table 5). These mice inoculated with ***prions*** from the GSS

patient JJ died after 171.+-.2.8 d (+-.SEM). The mean age of 247.+-.3 d

(\pm .SEM) at which these. . . days earlier than the age at which uninoculated controls developed signs of CNS dysfunction. Although the Tg(MHu2M-P101L) mice inoculated with ***prions*** from the sporadic CJD cases have a mean incubation time of 259. \pm .10 d (\pm .SEM) (n/n.sub.o= 12/15), these mice were 350. \pm .11. . . the time of death. The age of these mice prevented us from concluding whether they became ill from the inoculated ***prions*** or spontaneously as a result of the MHu2MPrP-P102L mutant protein.

DETD Our findings demonstrate that Hu ***prions*** from the GSS patient carrying the point mutation homologous to that in the transgene caused disease more rapidly than did wt Hu ***prions*** from sporadic cases of CJD. Conversely, the Hu ***prions*** from the GSS patient have failed to produce disease >280 d after inoculation in Tg(MHu2M)5376/Prnp.sup.0/0 mice (Table 6 Section C); whereas, Hu ***prions*** containing wt PrP.sup.Sc cause disease in Tg(MHu2M)5378/Prnp.sup.0/0 mice at .about.190 d (Table 6 Section B). The onset of illness in. . .

DETD Tg(MHu2M-P101L) mice inoculated with GSS ***prions*** exhibited spongiform degeneration and reactive astrocytic gliosis similar to uninoculated Tg(MHu2M-P101L) mice that developed CNS dysfunction spontaneously. However, the inoculated. . . accumulation was more intense in some gray matter regions such as the hippocampus in the Tg(MHu2M-P101L) mice inoculated with GSS ***prions*** than the uninoculated animals exhibiting spontaneous illness.

DETD . . . DeArmond S. J., and Prusiner, S. B. (1994). Serial transmission in rodents of neurologic disease from transgenic mice expressing mutant ***prion*** protein. Likewise, the brain of the GSS patient JJ from which the inoculum was derived contained relatively little or no. . . J., Poulter, M., Owen, F., Terwilliger, J. D., Westaway, D., Ott, J., and Prusiner, S. B. (1989). Linkage of a ***prion*** protein missense variant to Gerstmann-Straussler syndrome. Nature 338:342-345. On some occasions, a weak, diffuse band comigrating with PrP 27-30 has. . . CNS dysfunction. The relatively short incubation times in the Tg(MHu2M-P101L) 69/Prnp.sup.0/0 mice argue that the brain of JJ contained high ***prion*** titers even if PrP 27-30 was difficult to detect. From these results, we conclude that PrP.sup.Sc containing the P102L mutation. . .

DETD Transmission of Familial CJD (E200K) Human ***Prions*** To Tg(MHu2M) Mice

DETD . . . (\pm .SEM, n=10) for the LJ1 case and .about.160 d for the CA case. In contrast to the P102L mutation, Hu ***prions*** from patients who carried the E200K mutation caused disease as rapidly in Tg(MHu2M)5378/Prnp.sup.0/0 mice as Hu ***prions*** containing wtPrP.sup.Sc from sporadic CJD cases (Table 6 Section C).

CLM What is claimed is:

. . . codon of the PrP gene of the genetically diverse species; wherein the transgenic mouse is susceptible to infection with a ***prion*** which generally only infects an animal of the genetically diverse species due to the presence of said exogenous PrP gene; and; wherein the mouse exhibits symptoms of ***prion*** disease within about 200 days or less after inoculation with a ***prion*** which generally only infects an animal of the genetically diverse species.

4. A method of testing a sample for the presence of a ***prion*** , comprising: inoculating a transgenic with the sample, wherein the mouse has a genome comprised of: an ablated endogenous PrP gene. . . codon of the PrP gene of the genetically diverse species; wherein the transgenic mouse is susceptible to infection with a ***prion*** which generally only infects an animal of the genetically diverse species due to the presence of said exogenous PrP gene; wherein the transgenic mouse exhibits symptoms of ***prion*** disease within

about 200 days or less after inoculation with a ***prion*** which generally only infects an animal of the genetically diverse species; and observing the mouse in order to determine if the mouse develops symptoms of ***prion*** infection wherein the development of said symptoms indicates the presence of ***prions*** in said sample.

5. The method of claim 4, wherein the sample includes ***prions*** in a concentration in the range of 1 part per million or less.

6. The method of claim 4, wherein the sample includes ***prions*** in a concentration of one part per billion or less.

. . . codon of the PrP gene of the genetically diverse species; wherein the transgenic mouse is susceptible to infection with a ***prion*** which generally only infects an animal of the genetically diverse species due to the presence of said exogenous PrP gene; and; wherein the transgenic mouse exhibits symptoms of ***prion*** disease within about 200 days or less after inoculation with a ***prion*** which generally only infects an animal of the genetically diverse species; and observing the mouse in order to determine if the mouse develops symptoms of ***prion*** infection wherein the development of said symptoms indicates ***prion*** involvement in the death of said animal.

13. The method of determining the efficacy of a compound for the treatment of a ***prion*** related disease, comprising: inoculating a transgenic mouse with ***prions*** which are normally only infectious to a genetically diverse test animal selected from the group consisting of a cow, sheep, . . . codon of the PrP gene of the genetically diverse species; wherein the transgenic mouse is susceptible to infection with a ***prion*** which generally only infects an animal of the genetically diverse species due to the presence of said exogenous PrP gene; and; wherein the transgenic mouse exhibits symptoms of ***prion*** disease within about 200 days or less after inoculation with a ***prion*** which generally only infects an animal of the genetically diverse species; and administering the compound to the inoculated mouse; and. . . determine the efficacy of the compound in treating a disease which normally results from inoculation of the mouse with the ***prions*** .

=> s l11 and (PrPsc)

L13 237 L11 AND (PRPSC)

=> d ti so l-

YOU HAVE REQUESTED DATA FROM 237 ANSWERS - CONTINUE? Y/(N):y

L13 ANSWER 1 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Regional heterogeneity of cellular ***prion*** protein isoforms in the
mouse brain.

SO Brain, (September 2003) Vol. 126, No. 9, pp. 2065-2073. print.
ISSN: 0006-8950 (ISSN print).

L13 ANSWER 2 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Immunohistochemical comparison of anti- ***prion*** protein (PrP)
antibodies in the CNS of mice infected with scrapie.

SO Journal of Histochemistry and Cytochemistry, (August 2003) Vol. 51, No. 8,
pp. 1065-1071. print.
ISSN: 0022-1554 (ISSN print).

L13 ANSWER 3 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI Mapping the antigenicity of copper-treated cellular ***prion*** protein with the scrapie isoform.

SO CMLS Cellular and Molecular Life Sciences, (June 2003) Vol. 60, No. 6, pp. 1224-1234. print.
ISSN: 1420-682X.

L13 ANSWER 4 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI DIFFERENCES IN PrP TRANSCRIPTION AND TRANSLATION IN TWO MURINE MYELOMA CELL LINES.

SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002)
Vol. 2002, pp. Abstract No. 692.6. <http://sfn.scholarone.com>. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience.
Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.

L13 ANSWER 5 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Guanidine hydrochloride extraction and detection of ***prion*** proteins in mouse and hamster ***prion*** diseases by ELISA.

SO Journal of Pathology, (April 2003) Vol. 199, No. 4, pp. 534-541. print.
ISSN: 0022-3417 (ISSN print).

L13 ANSWER 6 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI CD21-positive follicular dendritic cells: A possible source of ***PrPSc*** in lymph node macrophages of scrapie-infected sheep.

SO American Journal of Pathology, (April 2003) Vol. 162, No. 4, pp. 1075-1081. print.
ISSN: 0002-9440 (ISSN print).

L13 ANSWER 7 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI ***Monoclonal*** antibodies inhibit ***prion*** replication and delay the development of ***prion*** disease.

SO Nature (London), (6 March 2003) Vol. 422, No. 6927, pp. 80-83. print.
ISSN: 0028-0836 (ISSN print).

L13 ANSWER 8 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Optimized overproduction, purification, characterization and high-pressure sensitivity of the ***prion*** protein in the native (PrPC-like) or amyloid (***PrPSc*** -like) conformation.

SO Biochimica et Biophysica Acta, (21 February, 2003) Vol. 1645, No. 2, pp. 228-240. print.
ISSN: 0006-3002 (ISSN print).

L13 ANSWER 9 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Detection of bovine spongiform encephalopathy, ovine scrapie ***prion*** -related protein (***PrPSc***) and normal PrPc by ***monoclonal*** antibodies raised to copper-refolded ***prion*** protein.

SO Biochemical Journal, (15 February, 2003) Vol. 370, No. 1, pp. 81-90. print.
ISSN: 0264-6021.

L13 ANSWER 10 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Acidic pH and detergents enhance in vitro conversion of human brain PrPC to a ***PrPSc*** -like form.

SO Journal of Biological Chemistry, (November 15, 2002) Vol. 277, No. 46, pp. 43942-43947. print.
CODEN: JBCHA3. ISSN: 0021-9258.

L13 ANSWER 11 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Brain biopsy in Creutzfeldt-Jakob disease: Evolution of pathological changes by ***prion*** protein immunohistochemistry.

SO Neuropathology and Applied Neurobiology, (August, 2002) Vol. 28, No. 4, pp. 314-324. print.

CODEN: NANEDL. ISSN: 0305-1846.

L13 ANSWER 12 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Differentiation of ***prion*** protein glycoforms from naturally
occurring sheep scrapie, sheep-passaged scrapie strains (CH1641 and
SSBP1), bovine spongiform encephalopathy (BSE) cases and Romney and
Cheviot breed sheep experimentally inoculated with BSE using two
monoclonal antibodies.
SO Acta Neuropathologica, (September, 2002) Vol. 104, No. 3, pp. 279-286.
print.
CODEN: ANPTAL. ISSN: 0001-6322.

L13 ANSWER 13 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Expression in E. coli and purification of recombinant fragments of wild
type and mutant human ***prion*** protein.
SO Neurochemistry International, (July, 2002) Vol. 41, No. 1, pp. 55-63.
print.
CODEN: NEUIDS. ISSN: 0197-0186.

L13 ANSWER 14 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Validation of a luminescence immunoassay for the detection of
PrPSc in brain homogenate.
SO Journal of Virological Methods, (March, 2002) Vol. 101, No. 1-2, pp.
79-84. print.
CODEN: JVMEDH. ISSN: 0166-0934.

L13 ANSWER 15 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Cellular ***prion*** protein (PrPc) is present on endothelial
microparticles in plasma of healthy blood donors.
SO Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 709a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology,
Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of
Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

L13 ANSWER 16 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI CD34+ cells from paroxysmal nocturnal hemoglobinuria patients are
deficient in surface expression of cellular ***prion*** protein
(PrPc).
SO Blood, (November 16, 2001) Vol. 98, No. 11 Part 2, pp. 119b-120b. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology,
Part 2. Orlando, Florida, USA. December 07-11, 2001. American Society of
Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

L13 ANSWER 17 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI A ***prion*** -specific immunological epitope.
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 1743.
print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San
Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.

L13 ANSWER 18 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI CNA42 ***monoclonal*** antibody identifies FDC as ***PrPSc***
accumulating cells in the spleen of scrapie affected sheep.
SO Veterinary Immunology and Immunopathology, (28 September, 2001) Vol. 82,
No. 1-2, pp. 1-8. print.
CODEN: VIIMDS. ISSN: 0165-2427.

L13 ANSWER 19 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI Scrapie ***prion*** protein accumulation by scrapie-infected neuroblastoma cells abrogated by exposure to a ***prion*** protein antibody.

SO Proceedings of the National Academy of Sciences of the United States of America, (July 31, 2001) Vol. 98, No. 16, pp. 9295-9299. print.
CODEN: PNASA6. ISSN: 0027-8424.

L13 ANSWER 20 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI Cellular ***prion*** protein status in sheep: Tissue-specific biochemical signatures.

SO Journal of General Virology, (August, 2001) Vol. 82, No. 8, pp. 2017-2024. print.
CODEN: JGVIAY. ISSN: 0022-1317.

L13 ANSWER 21 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI Expression of ***prion*** protein on endothelial cells.

SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 819a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

L13 ANSWER 22 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI 10E4 antigen of scrapie lesions contains an unusual nonsulfated heparan motif.

SO Journal of Biological Chemistry, (April 20, 2001) Vol. 276, No. 16, pp. 12539-12545. print.
CODEN: JBCHA3. ISSN: 0021-9258.

L13 ANSWER 23 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI In vivo conversion of cellular ***prion*** protein to pathogenic isoforms, as monitored by conformation-specific antibodies.

SO Journal of Biological Chemistry, (April 6, 2001) Vol. 276, No. 14, pp. 11265-11271. print.
CODEN: JBCHA3. ISSN: 0021-9258.

L13 ANSWER 24 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI Site-directed ***monoclonal*** antibody specifically recognizes ***PrPSc***.

SO Vox Sanguinis, (July, 2000) Vol. 78, No. Suppl. 1, pp. O057. print.
Meeting Info.: 26th Congress of the International Society of Blood Transfusion. Vienna, Austria. July 09-14, 2000. International Society of Blood Transfusion.
CODEN: VOSAAD. ISSN: 0042-9007.

L13 ANSWER 25 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI The first outbreak of scrapie in indigenous sheep in Norway.

SO Norsk Veterinærtidsskrift, (2000) Vol. 112, No. 5, pp. 376-380. print.
ISSN: 0332-5741.

L13 ANSWER 26 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI Molecular analysis of Irish sheep scrapie cases.

SO Journal of General Virology, (June, 2000) Vol. 81, No. 6, pp. 1621-1627. print.
CODEN: JGVIAY. ISSN: 0022-1317.

L13 ANSWER 27 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI A comparative study of immunohistochemical methods for detecting abnormal ***prion*** protein with ***monoclonal*** and polyclonal antibodies.

SO Journal of Comparative Pathology, (Jan., 2000) Vol. 122, No. 1, pp. 43-53. print.

CODEN: JCVPAR. ISSN: 0021-9975.

L13 ANSWER 28 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Antibody binding defines a structure for an epitope that participates in
the PrP^C fwdarw ***PrP^{Sc}*** conformational change.

SO Journal of Molecular Biology, (Nov. 5, 1999) Vol. 293, No. 4, pp. 855-863.
print.

CODEN: JMOBAK. ISSN: 0022-2836.

L13 ANSWER 29 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI A novel epitope for the specific detection of exogenous ***prion***
proteins in transgenic mice and transfected murine cell lines.

SO Virology, (March 1, 1999) Vol. 255, No. 1, pp. 26-31. print.

CODEN: VIRLAX. ISSN: 0042-6822.

L13 ANSWER 30 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Mapping the ***prion*** protein using recombinant antibodies.

SO Journal of Virology, (Nov., 1998) Vol. 72, No. 11, pp. 9413-9418. print.

CODEN: JOVIAM. ISSN: 0022-538X.

L13 ANSWER 31 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Synthetic peptide vaccines yield ***monoclonal*** antibodies to
cellular and pathological ***prion*** proteins of ruminants.

SO Journal of General Virology, (April, 1998) Vol. 79, No. 4, pp. 937-945.
print.

CODEN: JGVIAI. ISSN: 0022-1317.

L13 ANSWER 32 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI An immunological approach to ***prion*** diseases.

SO Medical Hypotheses, (Jan., 1998) Vol. 50, No. 1, pp. 85-90. print.

CODEN: MEHYDY. ISSN: 0306-9877.

L13 ANSWER 33 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Changes in the localization of brain ***prion*** proteins during
scrapie infection (Originally published in Issue 37, pages 1271-1280,
August 1987).

SO Neurology, (Jan., 1998) Vol. 50, No. 1, pp. 1271-1280. print.

CODEN: NEURAI. ISSN: 0028-3878.

L13 ANSWER 34 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI ***Prion*** (***PrP^{Sc}***)-specific epitope defined by a
monoclonal antibody.

SO Nature (London), (Nov. 6, 1997) Vol. 390, No. 6655, pp. 74-77. print.

CODEN: NATUAS. ISSN: 0028-0836.

L13 ANSWER 35 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI Immunohistochemical diagnosis of BSE and scrapie using ***monoclonal***
antibody.

SO Journal of Molecular Medicine (Berlin), (1997) Vol. 75, No. 7, pp. B177.
Meeting Info.: XIX Symposium of the International Association for
Comparative Research on Leukemia and Related Diseases. Heidelberg,
Germany. July 13-18, 1997.

ISSN: 0946-2716.

L13 ANSWER 36 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI ***Prion*** protein (Prp) synthetic peptides induce cellular Prp to
acquire properties of the scrapie isoform.

SO Proceedings of the National Academy of Sciences of the United States of
America, (1995) Vol. 92, No. 24, pp. 11160-11164.

CODEN: PNASA6. ISSN: 0027-8424.

L13 ANSWER 37 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI ATTEMPTS TO CONVERT THE CELLULAR ***PRION*** PROTEIN INTO THE SCRAPIE
ISOFORM IN CELL-FREE SYSTEMS.

SO Journal of Virology, (1992) Vol. 66, No. 10, pp. 6155-6163.
CODEN: JOVIAM. ISSN: 0022-538X.

L13 ANSWER 38 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI IMMUNOAFFINITY PURIFICATION AND NEUTRALIZATION OF SCRAPIE ***PRION***
INFECTIVITY.

SO Proceedings of the National Academy of Sciences of the United States of
America, (1988) Vol. 85, No. 18, pp. 6617-6621.
CODEN: PNASA6. ISSN: 0027-8424.

L13 ANSWER 39 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI PURIFICATION AND PROPERTIES OF THE CELLULAR AND SCRAPIE HAMSTER
PRION PROTEINS.

SO European Journal of Biochemistry, (1988) Vol. 176, No. 1, pp. 21-30.
CODEN: EJBCAI. ISSN: 0014-2956.

L13 ANSWER 40 OF 237 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI CHANGES IN THE LOCALIZATION OF BRAIN ***PRION*** PROTEINS DURING
SCRAPIE INFECTION.

SO Neurology, (1987) Vol. 37, No. 8, pp. 1271-1280.
CODEN: NEURAI. ISSN: 0028-3878.

L13 ANSWER 41 OF 237 CABA COPYRIGHT 2003 CABI on STN
TI Immunohistochemical detection and distribution of ***prion*** protein
in a goat with natural scrapie.

SO Journal of Veterinary Diagnostic Investigation, (2003) Vol. 15, No. 2, pp.
157-162. 20 ref. Publisher: American Association of Veterinary Laboratory
Diagnosticians. ISSN: 1040-6387

L13 ANSWER 42 OF 237 CABA COPYRIGHT 2003 CABI on STN
TI Validation of ***monoclonal*** antibody F99/97.6.1 for
immunohistochemical staining of brain and tonsil in mule deer (*Odocoileus
hemionus*) with chronic wasting disease.

SO Journal of Veterinary Diagnostic Investigation, (2002) Vol. 14, No. 1, pp.
3-7. 18 ref. ISSN: 1040-6387

L13 ANSWER 43 OF 237 CABA COPYRIGHT 2003 CABI on STN
TI ***Prion*** diseases: diagnosis and pathogenesis

Archives of Virology, Supplement 16.

SO Prion diseases: diagnosis and pathogenesis, (2000) pp. 290. Publisher:
Springer-Verlag Wien. ISBN: 3-211-83530-X

L13 ANSWER 44 OF 237 CABA COPYRIGHT 2003 CABI on STN
TI Scrapie and bovine spongiform encephalopathy: immunological properties and
diagnosis for food products.

SO Lait, (1996) Vol. 76, No. 6, pp. 571-578. 44 ref. ISSN: 0023-7302

L13 ANSWER 45 OF 237 CABA COPYRIGHT 2003 CABI on STN
TI Mites as vectors for scrapie.

SO Lancet (British edition), (1996) Vol. 347, No. 9008, pp. 1114. 5 ref.
ISSN: 0140-6736

L13 ANSWER 46 OF 237 CABA COPYRIGHT 2003 CABI on STN
TI Effect of scrapie infection on the activity of neuronal nitric-oxide
synthase in brain and neuroblastoma cells.

SO Journal of Biological Chemistry, (1996) Vol. 271, No. 28, pp. 16856-16861.
55 ref. ISSN: 0021-9258

L13 ANSWER 47 OF 237 CABA COPYRIGHT 2003 CABI on STN

TI Detection of species specific epitopes of mouse and hamster ***prion*** proteins (PrPs) by anti-peptide antibodies.

SO Archives of Virology, (1996) Vol. 141, No. 3/4, pp. 763-769. 24 ref. ISSN: 0304-8608

L13 ANSWER 48 OF 237 CABA COPYRIGHT 2003 CABI on STN

TI Transmission of fatal familial insomnia to laboratory animals.

SO Lancet (British edition), (1995) Vol. 346, No. 8974, pp. 569-570. 5 ref. ISSN: 0140-6736

L13 ANSWER 49 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Preparation of avian antibodies to mammalian ***prions***, immunoassay and test kit for the diagnosis of transmissible spongiform encephalopathy

SO Ger. Offen., 6 pp.
CODEN: GWXXBX

L13 ANSWER 50 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI On-column purification and refolding of recombinant bovine ***prion*** protein: using its octarepeat sequences as a natural affinity tag

SO Protein Expression and Purification (2003), 32(1), 104-109
CODEN: PEXPEJ; ISSN: 1046-5928

L13 ANSWER 51 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Generation of Antibodies Against ***Prion*** Protein by Scrapie-Infected Cell Immunization of PrP0/0 Mice

SO Hybridoma and Hybridomics (2003), 22(4), 263-266
CODEN: HHYYBF; ISSN: 1536-8599

L13 ANSWER 52 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Methods for identification of genes expressed during Xanthomonas campestris infection or colonization of bean plants using in situ induced antigen technology (ISIAT) and application to detection of microbial infection of animals

SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2

L13 ANSWER 53 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Preparation and uses of surrogate antibodies that mimic the structure, stability, and binding characteristics of a natural antibody

SO PCT Int. Appl., 136 pp.
CODEN: PIXXD2

L13 ANSWER 54 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Simple and specific detection of abnormal ***prion*** protein by laser-induced fluorescence immunoassay

SO Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), ANYL-014 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69EKY9

L13 ANSWER 55 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Rapid method of determining clearance of ***prion*** protein

SO U.S., 10 pp.
CODEN: USXXAM

L13 ANSWER 56 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Preparation of ***prion*** knocked-out myeloma cells and the use of the cells for production ***monoclonal*** antibody

SO Jpn. Kokai Tokkyo Koho, 13 pp.
CODEN: JKXXAF

L13 ANSWER 57 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Method for detecting pathogenic ***prion*** proteins by means of mass spectroscopy
SO U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO

L13 ANSWER 58 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Generation of hybrid cell lines to produce human ***monoclonal*** antibodies or fragments for diagnosis and therapy of infections and cancers
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2

L13 ANSWER 59 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Methods of inhibiting amyloid toxicity from amyloid deposit using agents binding certain integrins or integrin subunits
SO U.S. Pat. Appl. Publ., 41 pp.
CODEN: USXXCO

L13 ANSWER 60 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Synthetic immunogenic/non-deposit-forming polypeptides and peptides homologous to amyloid .beta., ***prion*** protein, amylin, .alpha.-synuclein, or polyglutamine repeats for induction of an immune response
SO PCT Int. Appl., 265 pp.
CODEN: PIXXD2

L13 ANSWER 61 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Methods and kits for proximity probing and their use in drug screening and detection of pathogens
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2

L13 ANSWER 62 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Immunoassay reagent and kit for measuring abnormal-type ***prion*** , and immunoassay method for measuring abnormal-type ***prion*** using reagent or kit
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF

L13 ANSWER 63 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Antibodies specific for human ***prions*** and use in conformation-dependent immunoassays for the determination of pathogenic ***prions***.
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW

L13 ANSWER 64 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Muscle sample prepared for ***prion*** assay
SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2

L13 ANSWER 65 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Device with chemical surface patterns
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2

L13 ANSWER 66 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Agent cleaving PrPC for treating or preventing ***prion*** infection
SO U.S. Pat. Appl. Publ., 21 pp.

CODEN: USXXCO

L13 ANSWER 67 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Methods for sterilizing preparations containing albumin
SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2

L13 ANSWER 68 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Method for detecting ***prion*** proteins in tissue samples
SO U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO

L13 ANSWER 69 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Methods for sterilizing biological materials
SO U.S. Pat. Appl. Publ., 22 pp.
CODEN: USXXCO

L13 ANSWER 70 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Method for testing the presence of ***prion*** proteins in tissue and culture samples and for identifying therapeutic agents
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2

L13 ANSWER 71 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Methods for sterilizing preparations of ***monoclonal*** immunoglobulins by irradiation
SO PCT Int. Appl., 108 pp.
CODEN: PIXXD2

L13 ANSWER 72 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Anti- ***prion*** antibodies for prophylaxis following ***prion*** exposure in mice
SO Neuroscience Letters (2003), 336(3), 185-187
CODEN: NELED5; ISSN: 0304-3940

L13 ANSWER 73 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Device and method of use for detection and characterization of pathogens and biological materials
SO U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 519,271.
CODEN: USXXCO

L13 ANSWER 74 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Selection of suitable ***monoclonal*** antibodies and optimization of the immunohistochemical method for detection of pathological ***prion*** protein in the brains of patients with sporadic Creutzfeldt-Jacob disease
SO Medicinski Razgledi (2002), 41(1), 3-12
CODEN: MRAZAM; ISSN: 0025-8121

L13 ANSWER 75 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Method of identifying a ligand for a target molecule
SO U.S. Pat. Appl. Publ., 35 pp.
CODEN: USXXCO

L13 ANSWER 76 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI ***Prion*** protein dimers useful for vaccination
SO Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW

L13 ANSWER 77 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI BSE, scrapie, and consumer safety
SO GIT Labor-Fachzeitschrift (2002), 46(9), 990-991

CODEN: GLFAF5

L13 ANSWER 78 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI ***Prion*** and viral clearance process for immunoglobulin preparations

SO Eur. Pat. Appl., 36 pp.

CODEN: EPXXDW

L13 ANSWER 79 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Anti-aggregating antibodies, a new approach towards treatment of conformational diseases

SO Current Medicinal Chemistry (2002), 9(19), 1737-1749

CODEN: CMCHE7; ISSN: 0929-8673

L13 ANSWER 80 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Immunoassay for the determination of brain-diseases from eye samples

SO PCT Int. Appl., 10 pp.

CODEN: PIXXD2

L13 ANSWER 81 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Immunoassay for the detection of ***prion*** proteins

SO PCT Int. Appl., 22 pp.

CODEN: PIXXD2

L13 ANSWER 82 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Chimeric protein comprising aggregating disease protein and membrane-localizing portion for expressed in cell or animal to identify therapeutic, prognostic and diagnostic agents for neurodegenerative diseases

SO PCT Int. Appl., 123 pp.

CODEN: PIXXD2

L13 ANSWER 83 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Competitive ***prion*** reagents containing Congo red derivatives and their application for diagnostics and raising antibodies for immunotherapy

SO Ger. Offen., 20 pp.

CODEN: GWXXBX

L13 ANSWER 84 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Thermostable proteases and apparatus for degradation of ***prions*** to prevent transmissible spongiform encephalopathy infection in mice

SO PCT Int. Appl., 41 pp.

CODEN: PIXXD2

L13 ANSWER 85 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Extracorporeal capturing of specific bio-macromolecular entities from extracellular body fluids

SO PCT Int. Appl., 59 pp.

CODEN: PIXXD2

L13 ANSWER 86 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Methods for conducting assays, and devices for use therein

SO PCT Int. Appl., 37 pp.

CODEN: PIXXD2

L13 ANSWER 87 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Immunoassay and test kit for the diagnosis of spongiform encephalopathy using microparticles, fluorescent dyes, and flow cytometry

SO Ger. Offen., 8 pp.

CODEN: GWXXBX

L13 ANSWER 88 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Antiaggregating antibody raised against human PrP 106-126 recognizes
pathological and normal isoforms of the whole ***prion*** protein
SO Cellular and Molecular Neurobiology (2002), Volume Date 2001, 21(6),
693-703
CODEN: CMNEDI; ISSN: 0272-4340

L13 ANSWER 89 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI ***Monoclonal*** antibody for distinguishing abnormal type
prion from normal type ***prion*** and immunoassay kit
SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW

L13 ANSWER 90 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Method of determining ***prion*** strain
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2

L13 ANSWER 91 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI A urine test for the diagnosis of ***prion*** diseases
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2

L13 ANSWER 92 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Test kit for detecting autoantibodies and cytokines as indicators of
infectious and inflammatory conditions
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2

L13 ANSWER 93 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Pharmaceutical compositions comprising a soluble laminin receptor
precursor or a compound which blocks the interaction of the laminin
receptor precursor and ***PrPSc*** or PrPc
SO U.S. Pat. Appl. Publ., 51 pp., Cont.-in-part of U. S. Ser. no. 424,754.
CODEN: USXXCO

L13 ANSWER 94 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Close vicinity of PrP expressing cells (FDC) with noradrenergic fibers in
healthy sheep spleen
SO Developmental Immunology (2001), 8(3-4), 235-241
CODEN: DEIME7; ISSN: 1044-6672

L13 ANSWER 95 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Luminescence-based multianalyte determination system and methods of
analysis
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2

L13 ANSWER 96 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Method for precipitating mono and multiple layers of organophosphoric and
organophosphonic acids and the salts thereof in addition to use thereof
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2

L13 ANSWER 97 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Adenoviral targeting and manipulation of immune system response using
targeting peptides
SO PCT Int. Appl., 86 pp.
CODEN: PIXXD2

L13 ANSWER 98 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Production of human ***monoclonal*** antibodies in human B-lymphocyte hybridomas expressing an ectopic telomerase gene
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2

L13 ANSWER 99 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Antibodies specific for ungulate ***prion*** proteins
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2

L13 ANSWER 100 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Analytical apparatus for instantaneous molecular detection with ligands
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

L13 ANSWER 101 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Antibodies to ***prion*** ***PrPSc*** peptide for diagnosis of bovine spongiform encephalopathy and Creutzfeldt-Jacob Disease
SO Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW

L13 ANSWER 102 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI ***Prion*** proteins and their use in diagnosis and treatment of retroviral infections
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2

L13 ANSWER 103 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Electronic-property probing of biological molecules at surfaces
SO U.S., 41 pp., Cont.-in-part of U.S. Ser. No. 804,883, abandoned.
CODEN: USXXAM

L13 ANSWER 104 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Antibody-coated adsorbents, column system having the adsorbents for hemodialysis or plasmapheresis, and therapy using the system
SO Jpn. Kokai Tokkyo Koho, 31 pp.
CODEN: JKXXAF

L13 ANSWER 105 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Methods and kits for proximity probing
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2

L13 ANSWER 106 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Protecting molecules in biologically derived compositions while treating with broad-spectrum pulsed light
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2

L13 ANSWER 107 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Specific antibodies for the detection of ***prionic*** protein
SO Veterinariya (Moscow, Russian Federation) (2001), (5), 23-27
CODEN: VETNAL; ISSN: 0042-4846

L13 ANSWER 108 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Apparatus for screening compound libraries using frontal chromatog. in combination with mass spectrometry
SO U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S. 6,054,047.
CODEN: USXXCO

L13 ANSWER 109 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Method for diagnosing a transmissible spongiform subacute encephalopathy caused by an unconventional transmissible agent strain in a biological sample using ***prion*** digestion and immunological identification of octapeptides

SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2

L13 ANSWER 110 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Immunofluorescent determination and differentiation of subcellular protein aggregates

SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2

L13 ANSWER 111 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Factors having ***prion*** -binding activity in serum and plasma and agents to detect transmissible spongiform encephalopathitis

SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2

L13 ANSWER 112 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Methods of inhibiting binding of .beta.-sheet fibril to RAGE, and consequences thereof

SO PCT Int. Appl., 174 pp.
CODEN: PIXXD2

L13 ANSWER 113 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI ***Monoclonal*** antibodies and antibody cocktail for detection of ***prion*** protein as an indication of transmissible spongiform encephalopathies

SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2

L13 ANSWER 114 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI ***Prion*** protein binding proteins and uses thereof

SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2

L13 ANSWER 115 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI ***Prion*** protein peptides and uses thereof

SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2

L13 ANSWER 116 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Vaccines against conformation-dependent protein and non-protein antigens

SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2

L13 ANSWER 117 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Method to type ***prion*** proteins and diagnostic and treatment agents

SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2

L13 ANSWER 118 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Blood serum sample treatment with complexing agent for isolation of ***prions*** and ***PrPSc***

SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2

L13 ANSWER 119 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN

TI Molecular analysis of Irish sheep scrapie cases. [Erratum to document

cited in CA133:133587]
SO Journal of General Virology (2000), 81(8), 2121
CODEN: JGVIAI; ISSN: 0022-1317

L13 ANSWER 120 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Removal of ***prions*** from blood, plasma and other liquids using
prion complexing agents
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2

L13 ANSWER 121 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Coated substrates for blood, plasma, or tissue washing and columns
equipped with these substrates
SO Ger. Offen., 30 pp.
CODEN: GWXXBX

L13 ANSWER 122 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Anti- ***prion*** antibody
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF

L13 ANSWER 123 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI ***Prion*** protein detection and isolation with Gln-Pro-His-binding
agents and uses thereof
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2

L13 ANSWER 124 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Identification of a highly immunogenic site on the murine ***prion***
protein
SO Alzheimer's Disease Review [Electronic Publication] (1999), 4, 13-18
CODEN: ADREFN; ISSN: 1093-5355
URL: <http://www.coa.uky.edu/ADReview/Vol14/Rubenstein.pdf>

L13 ANSWER 125 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Therapeutic preparation: ***monoclonal*** immunogenic protease (MIP)/
monoclonal immunogenic chymotrypsin (MIC)
SO Ger. Offen., 6 pp.
CODEN: GWXXBX

L13 ANSWER 126 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Methods using frontal chromatography-mass spectrometry for screening
compound libraries
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2

L13 ANSWER 127 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Frontal chromatog.-mass spectrometry apparatus for screening compound
libraries
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2

L13 ANSWER 128 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Validation of a Western immunoblotting procedure for bovine ***PrPSc***
detection and its use as a rapid surveillance method for the diagnosis of
bovine spongiform encephalopathy (BSE)
SO Acta Neuropathologica (1999), 98(5), 437-443
CODEN: ANPTAL; ISSN: 0001-6322

L13 ANSWER 129 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Expression of human PRP gene in prokaryotic cells using GST fusion protein

expression system
SO Zhonghua Shiyen He Linchuang Bingduxue Zazhi (1999), 13(2), 124-127
CODEN: ZSLZFS; ISSN: 1003-9279

L13 ANSWER 130 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Optical sensor unit and procedure for the ultrasensitive detection of
chemical or biochemical analytes
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW

L13 ANSWER 131 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Apparatus for screening compound libraries using frontal chromatog. in
combination with mass spectrometry
SO Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW

L13 ANSWER 132 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Assay for disease-related conformation of a protein
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2

L13 ANSWER 133 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Immunological detection of ***prions***
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2

L13 ANSWER 134 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Immunological detection of ***prions***
SO Eur. Pat. Appl., 35 pp.
CODEN: EPXXDW

L13 ANSWER 135 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Electronic-property probing and immobilization of biological molecules at
surfaces and biosensors containing them
SO PCT Int. Appl., 93 pp.
CODEN: PIXXD2

L13 ANSWER 136 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Pharmaceutical antigen/antibody preparation
SO Ger. Offen., 10 pp.
CODEN: GWXXBX

L13 ANSWER 137 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Pressure-mediated binding of biomolecular complexes
SO PCT Int. Appl., 89 pp.
CODEN: PIXXD2

L13 ANSWER 138 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Biological material free of viral and molecular pathogens and process for
its production
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2

L13 ANSWER 139 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Electrochemiluminescent labels having improved nonspecific binding
properties
SO PCT Int. Appl., 132 pp.
CODEN: PIXXD2

L13 ANSWER 140 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
TI Generation of ***monoclonal*** antibodies against ***prion***

- proteins by nucleic acid-mediated immunization of PrP0/0-mice
 SO Vaccines 97: Molecular Approaches to the Control of Infectious Diseases,
 [Annual Meeting on Modern Approaches to the Control of Infectious
 Diseases], 14th, Cold Spring Harbor, N. Y., Sept. 9-13, 1996 (1997),
 Meeting Date 1996, 265-272. Editor(s): Brown, Fred. Publisher: Cold
 Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y.
 CODEN: 64QNAJ
- L13 ANSWER 141 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
 TI ***Prion*** protein peptides PrP and assays for ***PrPSc*** and
 inhibitors of ***PrPSc*** formation
 SO PCT Int. Appl., 49 pp.
 CODEN: PIXXD2
- L13 ANSWER 142 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
 TI Methods of reducing apolipoprotein E4-induced inhibition of neuron
 remodeling by prevention of apolipoprotein E4 interaction with neuronal
 LDL receptor-related protein (LRP)
 SO PCT Int. Appl., 49 pp.
 CODEN: PIXXD2
- L13 ANSWER 143 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
 TI Antibodies specific for native ***PrPSc*** for therapy and analysis
 SO PCT Int. Appl., 100 pp.
 CODEN: PIXXD2
- L13 ANSWER 144 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
 TI ***Prion*** biology
 SO Prion Dis. Hum. Anim. (1992), 533-67. Editor(s): Prusiner, Stanley B.
 Publisher: Horwood, London, UK.
 CODEN: 60BWAD
- L13 ANSWER 145 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
 TI Modification and expression of ***prion*** proteins in cultured cells
 SO Prion Dis. Hum. Anim. (1992), 457-69. Editor(s): Prusiner, Stanley B.
 Publisher: Horwood, London, UK.
 CODEN: 60BWAD
- L13 ANSWER 146 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
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 their preparation and use
 SO PCT Int. Appl., 36 pp.
 CODEN: PIXXD2
- L13 ANSWER 147 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
 TI Molecular location of a species-specific epitope on the hamster scrapie
 agent protein
 SO Journal of Virology (1991), 65(7), 3667-75
 CODEN: JOVIAM; ISSN: 0022-538X
- L13 ANSWER 148 OF 237 CAPLUS COPYRIGHT 2003 ACS on STN
 TI On the biology of ***prions***
 SO Acta Neuropathologica (1987), 72(4), 299-314
 CODEN: ANPTAL; ISSN: 0001-6322
- L13 ANSWER 149 OF 237 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS
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 SO Clinical Application of Immunology, (2002) 1/2 (71-75).
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 ISSN: 1312-0832 CODEN: CAILBU

L13 ANSWER 150 OF 237 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

TI Two-dimensional mapping of three phenotype-associated isoforms of the ***prion*** protein in sporadic Creutzfeldt-Jakob disease.

SO Electrophoresis, (2002) 23/2 (347-355).

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ISSN: 0173-0835 CODEN: ELCTDN

L13 ANSWER 151 OF 237 MEDLINE on STN

TI Role of variant Creutzfeldt-Jakob disease for safety of treatment with blood components: screening of lymphatic tissue is a potential tool for risk assessment.

SO EUROPEAN JOURNAL OF HAEMATOLOGY, (2003 Jan) 70 (1) 11-6.

Journal code: 8703985. ISSN: 0902-4441.

L13 ANSWER 152 OF 237 MEDLINE on STN

TI Detection of pathologic ***prion*** protein in the olfactory epithelium in sporadic Creutzfeldt-Jakob disease.

SO NEW ENGLAND JOURNAL OF MEDICINE, (2003 Feb 20) 348 (8) 711-9.

Journal code: 0255562. ISSN: 1533-4406.

L13 ANSWER 153 OF 237 MEDLINE on STN

TI Detection of PrP(sc) in samples presenting a very advanced degree of autolysis (BSE liquid state) by immunocytochemistry.

SO JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (2003 Jan) 51 (1) 15-8.

Journal code: 9815334. ISSN: 0022-1554.

L13 ANSWER 154 OF 237 MEDLINE on STN

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SO Chembiochem, (2002 Aug 2) 3 (8) 717-25.

Journal code: 100937360. ISSN: 1439-4227.

L13 ANSWER 155 OF 237 MEDLINE on STN

TI Cellular ***prion*** protein is expressed on endothelial cells and is released during apoptosis on membrane microparticles found in human plasma.

SO TRANSFUSION, (2002 Mar) 42 (3) 334-42.

Journal code: 0417360. ISSN: 0041-1132.

L13 ANSWER 156 OF 237 MEDLINE on STN

TI Immunohistochemistry of ***PrPsc*** within bovine spongiform encephalopathy brain samples with graded autolysis.

SO JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (2001 Dec) 49 (12) 1519-24.

Journal code: 9815334. ISSN: 0022-1554.

L13 ANSWER 157 OF 237 MEDLINE on STN

TI Oxidative impairment in scrapie-infected mice is associated with brain metals perturbations and altered antioxidant activities.

SO JOURNAL OF NEUROCHEMISTRY, (2001 Nov) 79 (3) 689-98.

Journal code: 2985190R. ISSN: 0022-3042.

L13 ANSWER 158 OF 237 MEDLINE on STN

TI Autonomic nervous system innervation of lymphoid territories in spleen: a possible involvement of noradrenergic neurons for ***prion*** neuroinvasion in natural scrapie.

SO JOURNAL OF NEUROVIROLOGY, (2001 Oct) 7 (5) 447-53.

Journal code: 9508123. ISSN: 1355-0284.

L13 ANSWER 159 OF 237 MEDLINE on STN

TI Different levels of ***prion*** protein (PrPc) expression on hamster, mouse and human blood cells.
SO BRITISH JOURNAL OF HAEMATOLOGY, (2000 Aug) 110 (2) 472-80.
Journal code: 0372544. ISSN: 0007-1048.

L13 ANSWER 160 OF 237 MEDLINE on STN

TI Detection of bovine spongiform encephalopathy-specific PrP(Sc) by treatment with heat and guanidine thiocyanate.
SO JOURNAL OF VIROLOGY, (1999 Nov) 73 (11) 9386-92.
Journal code: 0113724. ISSN: 0022-538X.

L13 ANSWER 161 OF 237 MEDLINE on STN

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SO EMBO JOURNAL, (1999 Jun 15) 18 (12) 3193-203.
Journal code: 8208664. ISSN: 0261-4189.

L13 ANSWER 162 OF 237 MEDLINE on STN

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SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Aug 22) 272 (34) 21479-87.
Journal code: 2985121R. ISSN: 0021-9258.

L13 ANSWER 163 OF 237 MEDLINE on STN

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SO NATURE MEDICINE, (1996 Jan) 2 (1) 59-64.
Journal code: 9502015. ISSN: 1078-8956.

L13 ANSWER 164 OF 237 MEDLINE on STN

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SO DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (1993) 80 141-51. Ref: 20
Journal code: 0427140. ISSN: 0301-5149.

L13 ANSWER 165 OF 237 MEDLINE on STN

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SO JOURNAL OF IMMUNOLOGY, (1991 Nov 15) 147 (10) 3568-74.
Journal code: 2985117R. ISSN: 0022-1767.

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SO MONOGRAPHS IN PATHOLOGY, (1990) (32) 86-122. Ref: 171
Journal code: 0416716. ISSN: 0077-0922.

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SO CELL, (1990 Apr 6) 61 (1) 185-92.
Journal code: 0413066. ISSN: 0092-8674.

L13 ANSWER 168 OF 237 MEDLINE on STN

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SO PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, (1989) 317 583-600. Ref: 47
Journal code: 7605701. ISSN: 0361-7742.

L13 ANSWER 169 OF 237 MEDLINE on STN

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prion structure and biology.
SO CIBA FOUNDATION SYMPOSIUM, (1988) 135 239-60. Ref: 98
Journal code: 0356636. ISSN: 0300-5208.

L13 ANSWER 170 OF 237 MEDLINE on STN
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prion proteins.

SO JOURNAL OF VIROLOGY, (1988 May) 62 (5) 1558-64.
Journal code: 0113724. ISSN: 0022-538X.

L13 ANSWER 171 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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plasma membrane to a subset of early endosomes and the Golgi
SO JOURNAL OF NEUROCHEMISTRY, (OCT 2003) Vol. 87, No. 2, pp. 353-363.
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OXON, ENGLAND.
ISSN: 0022-3042.

L13 ANSWER 172 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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cases of bovine spongiform encephalopathy (BSE) and experimental BSE in
sheep
SO JOURNAL OF CLINICAL MICROBIOLOGY, (SEP 2003) Vol. 41, No. 9, pp.
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Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904
USA.
ISSN: 0095-1137.

L13 ANSWER 173 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
TI Generation of antibodies against ***prion*** protein by
scrapie-infected cell immunization of PrP0/0 mice
SO HYBRIDOMA AND HYBRIDOMICS, (AUG 2003) Vol. 22, No. 4, pp. 263-266.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY
10538 USA.
ISSN: 0272-457X.

L13 ANSWER 174 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (SEP 2003) Vol. 133, No. 3, pp.
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L13 ANSWER 175 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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scrapie-infected cells and in the brains of patients with
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SO FEBS LETTERS, (11 FEB 2003) Vol. 536, No. 1-3, pp. 61-65.
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NETHERLANDS.
ISSN: 0014-5793.

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prion disease in mice
SO JOURNAL OF NEUROSCIENCE RESEARCH, (15 JAN 2003) Vol. 71, No. 2, pp.
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NY 10158-0012 USA.
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L13 ANSWER 177 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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cells in lymphoid and neural tissues of naturally scrapie-affected sheep
by double-labeling immunohistochemistry
SO JOURNAL OF HISTOCHEMISTRY & CYTOCHEMISTRY, (OCT 2002) Vol. 50, No. 10, pp.
1357-1370.
Publisher: HISTOCHEMICAL SOC INC, UNIV WASHINGTON, DEPT BIOSTRUCTURE, BOX
357420, SEATTLE, WA 98195 USA.
ISSN: 0022-1554.

L13 ANSWER 178 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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SO CURRENT BIOLOGY, (2 APR 2002) Vol. 12, No. 7, pp. 523-530.
Publisher: CELL PRESS, 1100 MASSACHUSETTES AVE., CAMBRIDGE, MA 02138 USA.
ISSN: 0960-9822.

L13 ANSWER 179 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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prion infectivity
SO NATURE, (16 AUG 2001) Vol. 412, No. 6848, pp. 739-743.
Publisher: MACMILLAN PUBLISHERS LTD, PORTERS SOUTH, 4 CRINAN ST, LONDON N1
9XW, ENGLAND.
ISSN: 0028-0836.

L13 ANSWER 180 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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prion protein
SO PROTEIN SCIENCE, (APR 2001) Vol. 10, No. 4, pp. 854-863.
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11724 USA.
ISSN: 0961-8368.

L13 ANSWER 181 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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SO TRANSFUSION MEDICINE, (FEB 2001) Vol. 11, No. 1, pp. 3-14.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE,
OXON, ENGLAND.
ISSN: 0958-7578.

L13 ANSWER 182 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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mononuclear cells but not platelets of normal and scrapie-infected sheep
SO HAEMATOLOGICA, (FEB 2001) Vol. 86, No. 2, pp. 146-153.
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ITALY.
ISSN: 0390-6078.

L13 ANSWER 183 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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SO JOURNAL OF BIOLOGICAL CHEMISTRY, (23 JUN 2000) Vol. 275, No. 25, pp.
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PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.

L13 ANSWER 184 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
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SO IMMUNOLOGIC RESEARCH, (MAR 2000) Vol. 21, No. 2-3, pp. 265-278.
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07512.

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SO CURRENT SCIENCE, (25 AUG 1999) Vol. 77, No. 4, pp. 508-514.

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ISSN: 0011-3891.

L13 ANSWER 186 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI Immune surveillance and antigen conformation determines humoral immune response to the ***prion*** protein immunogen

SO JOURNAL OF NEUROVIROLOGY, (AUG 1999) Vol. 5, No. 4, pp. 401-413.

Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.

ISSN: 1355-0284.

L13 ANSWER 187 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI Characterization of antibodies raised against bovine-PrP-peptides

SO JOURNAL OF NEUROVIROLOGY, (JUN 1999) Vol. 5, No. 3, pp. 300-307.

Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.

ISSN: 1355-0284.

L13 ANSWER 188 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI Cellular ***prion*** proteins of mammalian species display an intrinsic partial proteinase K resistance

SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (30 DEC 1998) Vol. 253, No. 3, pp. 693-702.

Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.

ISSN: 0006-291X.

L13 ANSWER 189 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI Changes in the localization of brain ***prion*** proteins during scrapie infection (Reprinted from Neurology, vol 37, pg 1271-1280, 1987)

SO NEUROLOGY, (JAN 1998) Vol. 50, No. 1, pp. A1-A10.

Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106.

ISSN: 0028-3878.

L13 ANSWER 190 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI A conformational transition at the N terminus of the ***prion*** protein features in formation of the scrapie isoform

SO JOURNAL OF MOLECULAR BIOLOGY, (31 OCT 1997) Vol. 273, No. 3, pp. 614-622.

Publisher: ACADEMIC PRESS LTD, 24-28 OVAL RD, LONDON, ENGLAND NW1 7DX.

ISSN: 0022-2836.

L13 ANSWER 191 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI Antigenic features of ***prion*** proteins of sheep and of other mammalian species

SO JOURNAL OF IMMUNOLOGICAL METHODS, (22 AUG 1997) Vol. 207, No. 1, pp. 89-101.

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.

ISSN: 0022-1759.

L13 ANSWER 192 OF 237 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

TI COOH-terminal sequence of the cellular ***prion*** protein directs subcellular trafficking and controls conversion into the scrapie isoform
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (18 MAR 1997) Vol. 94, No. 6, pp. 2333-2338.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418.
ISSN: 0027-8424.

L13 ANSWER 193 OF 237 USPATFULL on STN
TI Method of concentrating proteins from serum

L13 ANSWER 194 OF 237 USPATFULL on STN
TI Methods, reagents, kits and apparatus for protein function analysis

L13 ANSWER 195 OF 237 USPATFULL on STN
TI Staged assembly of nanostructures

L13 ANSWER 196 OF 237 USPATFULL on STN
TI Synthetic immunogenic but non-deposit-forming polypeptides and peptides homologous to amyloid beta, ***prion*** protein, amylin, alpha-synuclein, or polyglutamine repeats for induction of an immune response thereto

L13 ANSWER 197 OF 237 USPATFULL on STN
TI Ligands specific for an isoform of the ***prion*** protein

L13 ANSWER 198 OF 237 USPATFULL on STN
TI Antibodies specific for ungulate PrP

L13 ANSWER 199 OF 237 USPATFULL on STN
TI Surface simulation synthetic peptides useful in the treatment of hyper-variable viral pathogens

L13 ANSWER 200 OF 237 USPATFULL on STN
TI Methods of detecting a cell

L13 ANSWER 201 OF 237 USPATFULL on STN
TI Nucleic acid molecules capable of distinguishing the isoforms PrPc and ***PrPSc*** of ***prion*** proteins and processes for their production

L13 ANSWER 202 OF 237 USPATFULL on STN
TI Novel methods for down-regulation of amyloid

L13 ANSWER 203 OF 237 USPATFULL on STN
TI Agents and compositions and methods utilizing same useful in diagnosing and/or treating or preventing plaque forming

L13 ANSWER 204 OF 237 USPATFULL on STN
TI Encapsulation of plasmid DNA (lipogenes.TM.) and therapeutic agents with nuclear localization signal/fusogenic peptide conjugates into targeted liposome complexes

L13 ANSWER 205 OF 237 USPATFULL on STN
TI Antibodies specific for ungulate PrP

L13 ANSWER 206 OF 237 USPATFULL on STN
TI Genetically modified cows having reduced susceptibility to mad cow disease

L13 ANSWER 207 OF 237 USPATFULL on STN

TI Early pre-symptomatic ***prion*** diagnostic blood test for encephalopathies

L13 ANSWER 208 OF 237 USPATFULL on STN

TI Aptamers containing sequences of nucleic acid or nucleic acid analogues bound homologously, or in novel complexes

L13 ANSWER 209 OF 237 USPATFULL on STN

TI Methods and compositions for detection of disease

L13 ANSWER 210 OF 237 USPATFULL on STN

TI Sodium dodecyl sulfate compositions for inactivating ***prions***

L13 ANSWER 211 OF 237 USPATFULL on STN

TI Novel method for down-regulation of amyloid

L13 ANSWER 212 OF 237 USPATFULL on STN

TI " ***PRIONINS*** ", HIGHLY SPECIFIC MARKERS FOR NONINVASIVE PRE-SYMPTOMATIC DETECTION OF TSE DISEASES, AND TARGETS FOR THERAPEUTIC REAGENTS TO PREVENT AND CONTROL TSE DISEASES IN ANIMALS AND HUMANS

L13 ANSWER 213 OF 237 USPATFULL on STN

TI Antibodies specific for native ***PrPSc***

L13 ANSWER 214 OF 237 USPATFULL on STN

TI Discordant helix stabilization for prevention of amyloid formation

L13 ANSWER 215 OF 237 USPATFULL on STN

TI Conformational and topological protein regulation

L13 ANSWER 216 OF 237 USPATFULL on STN

TI Therapeutic agents and methods of use thereof for treating an amyloidogenic disease

L13 ANSWER 217 OF 237 USPATFULL on STN

TI ***Prion*** isomers, methods of making, methods of using, and compositions and products comprising ***prion*** isomers

L13 ANSWER 218 OF 237 USPATFULL on STN

TI Chaperones capable of binding to ***prion*** proteins and distinguishing the isoforms PrPc and ***PrPSc***

L13 ANSWER 219 OF 237 USPATFULL on STN

TI Inhibitors of IAPP fibril formation and uses thereof

L13 ANSWER 220 OF 237 USPATFULL on STN

TI Modulators of amyloid aggregation

L13 ANSWER 221 OF 237 USPATFULL on STN

TI Methods and compositions for the treatment and/or diagnosis of neurological diseases and disorders

L13 ANSWER 222 OF 237 USPATFULL on STN

TI Antibodies specific for native ***PrPSc***

L13 ANSWER 223 OF 237 USPATFULL on STN

TI Antiseptic compositions for inactivating ***prions***

L13 ANSWER 224 OF 237 USPATFULL on STN

TI ***Prion*** -binding activity in serum and proteins

L13 ANSWER 225 OF 237 USPATFULL on STN
TI ***Prion*** -binding activity in serum and plasma

L13 ANSWER 226 OF 237 USPATFULL on STN
TI Food additives which affect conformationally altered proteins

L13 ANSWER 227 OF 237 USPATFULL on STN
TI Modulators of amyloid aggregation

L13 ANSWER 228 OF 237 USPATFULL on STN
TI Antibodies specific for native ***PrPSc***

L13 ANSWER 229 OF 237 USPATFULL on STN
TI Correction of genetic defects using chemical chaperones

L13 ANSWER 230 OF 237 USPATFULL on STN
TI Assay for disease related conformation of a protein

L13 ANSWER 231 OF 237 USPATFULL on STN
TI Assay for disease related conformation of a protein and isolating same

L13 ANSWER 232 OF 237 USPATFULL on STN
TI Clearance and inhibition of conformationally altered proteins

L13 ANSWER 233 OF 237 USPATFULL on STN
TI Method of detecting ***prions*** in a sample and transgenic animal used for same

L13 ANSWER 234 OF 237 USPATFULL on STN
TI Correction of genetic defects using chemical chaperones

L13 ANSWER 235 OF 237 USPATFULL on STN
TI Assay for disease related conformation of a protein

L13 ANSWER 236 OF 237 USPATFULL on STN
TI A.beta. peptides that modulate .beta.-amyloid aggregation

L13 ANSWER 237 OF 237 USPATFULL on STN
TI Formation and use of ***prion*** protein (PRP) complexes